SOME APPLICATIONS OF THE SYNTHETIC POTENTIAL OF DIVERSELY SUBSTITUTED AZOLES

BY

KATHLEEN S. LAURENZO

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To Chip

For being there.

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Abstract of Dissertation Presented to the Graduate School of the University of Florida in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

SOME APPLICATIONS OF THE SYNTHETIC POTENTIAL OF DIVERSELY SUBSTITUTED AZOLES

BY

Kathleen S. Laurenzo

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Chairman: Alan R. Katritzky
Major Department: Chemistry

Some diverse features of azole chemistry have been studied in this investigation. A series of novel diaryl heterocyclic carbinols based on the isothiazole, thiazole and thiadiazole ring systems were prepared and tested as fungicides in the ergosterol biosynthesis inhibitor class. During the course of these syntheses, we have developed an improved method for the lithiation and functionalization of isothiazole in the 5-position. We have also developed a general method for the selective functionalization in the 5-position of the unsubstituted thiazole ring. This was accomplished by protection of the 2-position, lithiation and functionalization followed by deprotection.

Molecular orbital calculations were used to gain insight into the reasons why some compounds of this type are active as fungicides while other very similar compounds are not. We found that a correlation exists between biological activity and electron density at the β-nitrogen and made use

of such calculations to predict the activity of the compounds we prepared, and to identify new synthetic targets. Based on these results, some thiazole compounds with electron releasing groups at the 2-position were synthesized and submitted for testing.

We have also examined the base-catalyzed reaction of N-amino azoles with nitroaromatics. The reaction represents an extension of Makosza's vicarious nucleophilic substitution of hydrogen in which the azole ring serves the dual function of both activating and leaving group. In this investigation, we have demonstrated that direct amination of nitroaromatics can be accomplished conveniently and in good yields by a vicarious substitution sequence using 4-amino-1,2,4-triazoles. The reaction is highly regiospecific, affording 4-nitroanilines exclusively, and is compatible with a variety of other substituents on the aromatic ring. Additionally, N-substituted 4-nitroanilines can be readily prepared using 4-alkylamino-1,2,4-triazoles as the aminating agent. The latter were easily prepared by reductive condensation of 4-amino-1,2,4-triazole and the corresponding aldehydes or ketones in high yields. The vicarious nucleophilic amination reaction was found to be general for nitrosubstituted aromatics.

CHAPTER I

GENERAL INTRODUCTION

Azoles are aromatic five-membered rings containing one or more heteroatoms, at least one of which is a nitrogen. The simplest azole, pyrrole, can be considered to be derived from benzene by the replacement of a CH=CH group by NH. Azoles with heteroatoms in the 1,2 or 1,3 positions can be considered to be derived from benzene by the replacement of a CH group by a nitrogen atom and replacement of a CH=CH group by another heteroatom (O, S, or N-R). The chemistry of the azoles is varied, depending on the nature and position of the heteroatoms in the ring and any substitutents which may be present. In general, azoles have the potential to undergo a wide variety of reactions at heteroatoms, at ring carbons and at substituents, though the chemistry of each ring system is different.

Since azoles (other than pyrrole) always contain at least one pyridine-like nitrogen, the chemistry of the azoles is in some respects similar to that of pyridine; the pyridine-like nitrogen can react with electrophilic reagents such as protons, metal ions and alkylating agents.

Ring carbons can undergo nucleophilic attack in reactions similar to those of pyridine. Electrophilic attack can also occur at ring carbons; nitration, halogenation and other electrophilic substitution reactions of azoles are known, though the reactivity varies a great deal. Azoles generally do not undergo electrophilic attack at oxygen, sulfur or N-R groups.

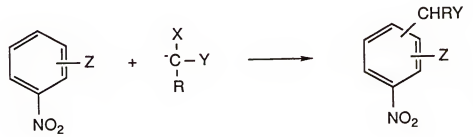
Azoles containing pyrrole-like NH groups are weak acids and can be deprotonated in the presence of strong bases. Ring C-H groups can also be deprotonated; base catalyzed hydrogen exchange in azoles is often a facile process [74AHC(16)1]. Metallation of azoles followed by reaction with an electrophile is a well-known method of functionalizing various azole rings [79OR1]. There are examples of the deprotonation of α-alkyl groups as well [73JOC3318, 83T4133, 86JOC3897, 87JCS(P1)].

In general, functional groups present on the azole rings undergo their characteristic reactions, although not all reaction conditions are compatible with a given ring system.

In the two broad categories of the present work, we have utilized the widely varying reactivity of azoles in order to accomplish specific synthetic objectives. In Chapter II, we describe the use of substituted and unsubstituted azoles in the synthesis of compounds expected to have a particular type of biological activity, namely fungitoxic compounds that have potential use as crop

protection chemicals. The ability of the pyridine-like nitrogen to complex with a ferric ion at the active site of an enzyme is the key to the biological activity of these compounds. Also, to promote binding at the active site, a large lipophilic substituent at the positon β to the nitrogen atom is required. A series of novel compounds based on the isothiazole, thiazole and thiadiazole rings were prepared and submitted for biological testing as fungicides.

In Chapter III we have examined azoles with an N-amino group in a base-catalyzed reaction with nitroaromatics, and the ability of the N-aminoazole to transfer its amino group to the aromatic ring under these conditions. The reaction was predicted by analogy to the vicarious nucleophilic substitution of hydrogen in nitroarenes by carbon nucleophiles as described by Makosza et. al. [e.g. 78TL3495, 84JOC1488]. Makosza's reaction (illustrated in Scheme 1) involves the addition of a carbanion bearing a leaving group (X) and an activating group (Y) to an aromatic ring. The intermediate Meisenheimer complex undergoes base-catalyzed β-elimination of HX to form the substituted product(s).



Scheme 1

Two features of azole chemistry made it feasible to use an azole-containing nucleophile in reactions of this type: first, the ability of the heterocyclic ring to stabilize an adjacent anion, and second, its ability to act as a leaving group (due to the relatively low pKa of the pyrrole-like NH). Thus, we envisioned that the heterocyclic ring could serve the functions of both the activating group and the leaving group, and the net result would be the transfer of the N-substituent from the azole to an aromatic ring.

Thus in this thesis the fundamental physical chemical properties of azoles were exploited to achieve widely different synthetic objectives. This was possible due to the fact that azoles can show diversely different reactivities depending on the nature of the nitrogen atom(s) (whether pyridine-like or pyrrole-like), the nature and position of other heteroatoms and the presence of ring substituents.

CHAPTER II

ERGOSTEROL BIOSYNTHESIS INHIBITING FUNGICIDES

2.1 Introduction

2.1.1 Background

The azole fungicides are a class of compounds introduced in the 1960s which quickly became widely used in food crops where fungal diseases, if left unchecked, take a very great toll. They are sometimes referred to as "super fungicides" because of their broad spectrum of activity and high level of effectiveness at low application rates. The compounds interfere with the steroid biosynthetic pathway of the fungus (shown in Figure 2.1) by inhibiting a particular cytochrome P450 enzyme [83MI1, 83MI2, 84MI1, 84MI2, 84MI3]. This enzyme catalyzes the conversion of 24-methylene-24,25-dihydrolanosterol (1) to the demethylated derivative 2. Thus, the concentration of 1 increases and that of the final product ergosterol (3), an essential component of the cell wall [84MI1], is depleted. The cell wall becomes weak and finally begins to leak, leading to cell death.

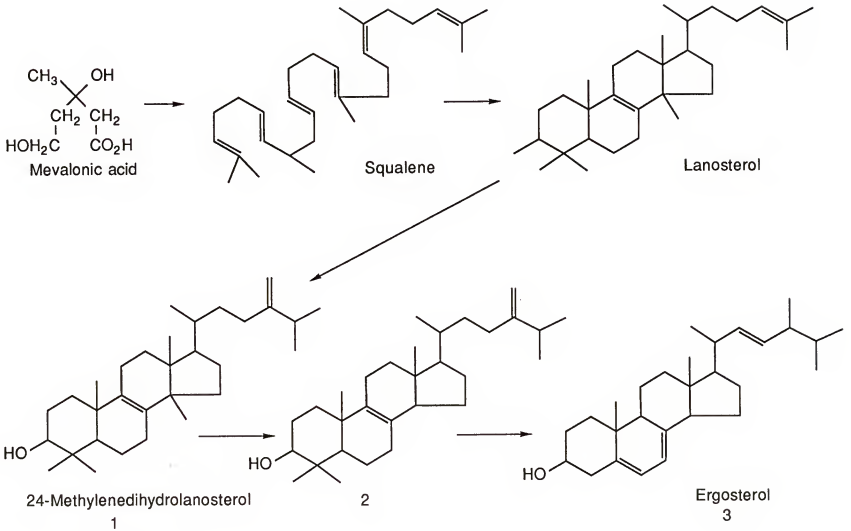
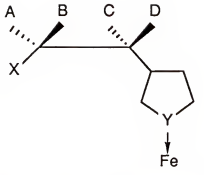


Figure 2.1 Brief Schematic of Biosynthesis of Ergosterol

Cytochromes P450 are ubiquitous in nature; the two main functions of these enzymes are the detoxification of xenobiotic compounds and the catalysis of certain reactions in steroid biosynthesis. Cytochrome P450 is a mixed function oxidase, i. e. it catalyzes the reaction between molecular oxygen and a substrate such that one oxygen atom is inserted into the substrate and the other is reduced to water. Thus, the common feature in all the P450 reactions is that the substrate is hydroxylated in the first step. Nearly all plants and animals utilize P450 enzymes, but since the biosynthetic pathways differ from species to species, a certain amount of specificity is inherent. Thus, a compound can be toxic to a fungus while the plant on which it is sprayed remains unaffected.

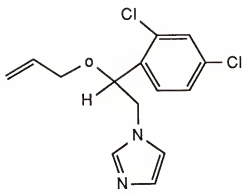
The general structural requirements for this class of inhibitors [84MI2] are shown in Figure 2.2. They include a lipophilic backbone and polar group necessary for recognition and binding at the active site. The critical feature for enzyme inactivation, however, is the presence of a nitrogen β to the ring fusion point. The unshared pair of electrons on the pyridine-like nitrogen complex with an Fe^{III} in the heme prosthetic group in the active site of the enzyme, preventing binding of the natural substrate.



A, B, C, D = Lipophilic backbone
X = Polar group

Figure 2.2 Model P-450 14-Demethylase Inhibitor

Some examples of commercial azole fungicides of the ergosterol biosynthesis inhibitor class are shown in Figure 2.3. Most of the EBI fungicides on the market today are based on the imidazole (e.g. 4) or on the 1,2,4-triazole ring systems (e.g. 5, 6) (Figure 2.3). A closely related compound with the same mode of action [72BBR2048] is the Eli Lilly product Triarimol (7), a pyrimidine with structural features similar to the model demethylase inhibitor shown in Figure 2.2. The fungicidal activity of compounds of general type 8 (Figure 2.4) containing 5- and 6-membered nitrogen-containing heterocycles (pyridine, pyrazine, pyridazine, imidazole and triazole) have been evaluated [84MI1], but there are no reports of such compounds based on heterocycles containing both nitrogen and sulfur (e.g. thiazole, isothiazole, thiadiazoles).



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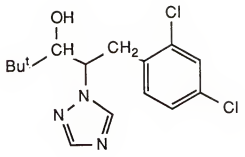
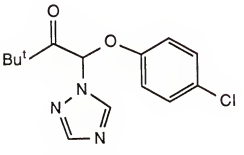


Vigil

5



Triadimefon

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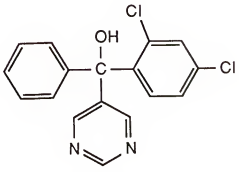

Triarimol

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Figure 2.3 Examples of Commercial EBI Fungicides

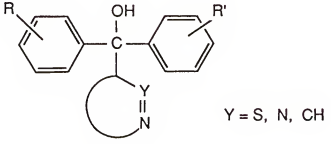

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Figure 2.4 Generalized Structure of the Proposed Compounds

2.1.2 Aim of the Work

The aim of the present work was to synthesize novel compounds of general structure 8 containing the heterocyclic ring systems thiazole, isothiazole and 1,2,3-thiadiazole, in order to evaluate their fungicidal activity. We chose Triarimol (7) as our model compound because there are two obvious disconnections suggesting convenient synthetic routes: the addition of a heterocyclic anion to a substituted benzophenone, or the addition of two moles of a Grignard reagent to a heterocyclic carboxylic ester or acid chloride.

2.1.3 Literature Review and Strategic Plan

Thiazoles. A search of Chemical Abstracts from 1927 to the present revealed no examples of otherwise unsubstituted thiazoles with a tertiary carbinol group in the 5-position (the only position which allows for a β-nitrogen). Based on literature analogies, two approaches were considered for the alkylation of the 5-postion of thiazole. For example, 5-bromo-4-methylthiazole has been treated with Mg under entrainment conditions to yield the corresponding Grignard reagent [52JA6260] which was then reacted with benzaldehyde to give the secondary carbinol. The first approach, then, was to attempt the analogous reaction with thiazole itself; this reaction has not been reported.

Direct lithiation of the thiazole nucleus affords the 2-lithio derivative [84MI4]; if the 2-position is blocked, lithiation can occur at the 5-position [84MI4, 73JOC3316]. Thus, the second possible approach to the preparation of 5-substituted thiazole carbinols was to protect the 2-position; after lithiation and substitution in the 5-position, the blocking group would be eliminated. Such an approach was previously used by Noyce and Fike [73JOC3316] to prepare a secondary 2-chlorothiazolyl-5-carbinol; the chloro substituent was removed by treatment with zinc and acetic acid.

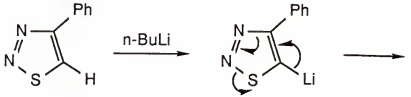
Isothiazoles. Carbinol substitution in either the 4- or 5-position would give a β-nitrogen. The only reported examples of tertiary carbinols based on the isothiazole ring are α,α-dimethyl-4- and 5-isothiazolemethanols which were prepared for a mechanistic study [75JOC3381]. The 5-isomer was prepared by direct lithiation of the isothiazole nucleus followed by addition of acetone. Isothiazole is well known to be converted by n-butyllithium into isothiazolyl-5-lithium [64JCS446], and there are a number of examples in the literature of the preparation of secondary carbinols by this method [68JCS(C)611, 75JHC49, 84JMC1245]. The yields in these reactions were moderate at best, however, and often quite poor.

The α,α-dimethyl-4-isothiazolemethanol [75JOC3381] was prepared by the addition of two moles of methyl Grignard

reagent to methyl isothiazole-4-carboxylate in reasonable yield. However, the synthesis of the ester [75JOC3381] was quite difficult, involving the oxidative degradation of 5-aminobenz[d]isothiazole (itself prepared by a multistep sequence in low overall yield [59JCS3061]) to the 4,5-dicarboxylic acid, which was in turn was decarboxylated to the monoacid, followed by esterification. Isothiazole-3-carboxylic acid can be prepared by the oxidation of 3-methylisothiazole [72AHC(14)1], but there is no convenient route to the 4-methyl compound. Another possible route to the 4-acid starts from the 4-bromo compound. Displacement of the bromo substituent by cyanide ion, followed by hydrolysis and esterification would give the 4-ester. This route has been used to prepare methyl 5-methyl-4-isothiazolecarboxylate [63JCS2032]. Although the 4-position of isothiazole is electrophilic, isothiazole itself does not undergo bromination well [72AHC(14)1]; 4-bromoisothiazole has been prepared from isothiazole by sequential nitration and reduction to the 4-amino compound followed by a Sandmeyer reaction [64JCS446]. Thus, all routes to the 4-substituted compounds are tedious, and we concentrated our initial efforts toward the synthesis of the 5-substituted compounds.

Thiadiazoles. No tertiary carbinols based on any of the isomeric thiadiazoles have been reported. For the 1,2,3-thiadiazole ring, substitution in either the 4- or 5-position would give a β-nitrogen.

Direct lithiation of the 1,2,3-thiadiazole nucleus has not been reported. It has been shown that 4-substituted 1,2,3-thiadiazoles undergo fragmentation in the presence of n-butyllithium by the mechanism shown in Scheme 2.1 [68CJC1057]; indeed, the reaction is a good general synthesis for alkynyl thioethers. Recently, however, the first example of lithiation of a 1,2,3-thiadiazole derivative was reported; 4-phenyl-1,2,3-thiadiazole was lithiated using LDA and trapped in situ by trimethylsilyl chloride in 55% yield [85S945]. In addition, 5-phenyl-1,2,3-thiadiazole has been alkylated at the 4-position by treatment with methyllithium followed by methyl iodide [68CJC1057].



$$N_2 + Ph-C\equiv C-S^-Li^+ \xrightarrow{CH_3I} Ph-C\equiv C-S-CH_3$$

Scheme 2.1

Thus, two routes were considered for the synthesis of 1,2,3-thiadiazoles of type 8. The first involved the addition of two moles of aryl Grignard reagent to a suitable

1,2,3-thiadiazole-5-carboxylate. The other possibility was to place a removable group at one position so as to enable lithiation and alkylation at the other position, followed by removal of the original group. A good candidate for such a removable substituent was the carboxylic acid group, as both 4- and 5-carboxylic acid derivatives of 1,2,3-thiadiazole readily undergo decarboxylation [68CJC1057].

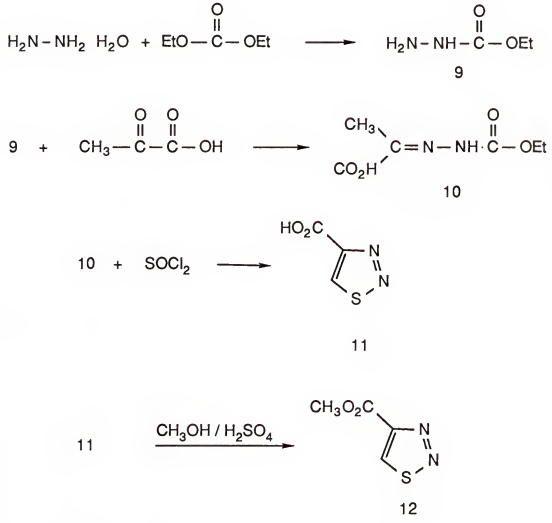
2.2 Results and Discussion

2.2.1 Compounds Based on 1,2,3-Thiadiazole

The cyclization of tosyl or acyl hydrazones containing an α-methylene group in the presence of thionyl chloride is a convenient general method for the synthesis of 1,2,3-thiadiazoles. The reaction was discovered by Hurd and Mori in 1955 [55JA5359] and extended by other groups [65JCS5166, 68CJC1057]; however, the mechanism of this reaction is still not well understood [69JHC239].

Methyl 1,2,3-thiadiazole-4-carboxylate was synthesized in 82% overall yield by the reaction sequence shown in Scheme 2.2 [55JA5359]. Pyruvic acid was treated with ethoxycarbonyl hydrazine (9) to form the hydrazone 10 in quantitative yield. Hydrazone 10 was cyclized in thionyl chloride at 0°C overnight followed by 8 hours at room temperature to give crude 1,2,3-thiadiazole-4-carboxylic

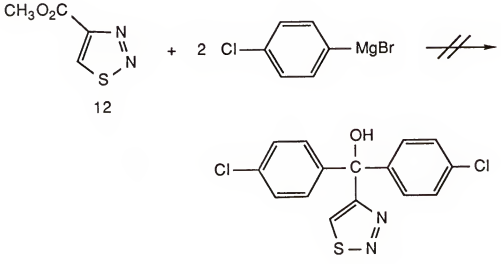
acid (11) in 89% yield. Acid catalyzed esterification in methanol then gave methyl 1,2,3-thiadiazole-4-carboxylate (12) in 92% yield.



Scheme 2.2

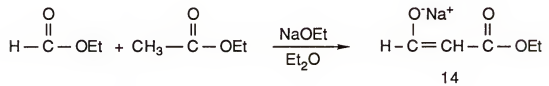
Reaction of the 4-ester 12 at -78°C with the Grignard reagent derived from 4-bromochlorobenzene failed to produce any of the desired product 13. The product mixture

consisted of unreacted ester (36%), 4,4'-dichlorobiphenyl (40%) and a small amount of what is suspected to be the intermediate ketone. There was much decomposition, increasing at higher temperatures. A likely cause of the failure of this reaction was that the Grignard reagent acted as a base toward H5, initiating the ring opening of the thiadiazole (c.f. Scheme 2.1).



Ethyl 1,2,3-thiadiazole-5-carboxylate (16) was prepared in 13% overall yield by the reaction sequence shown in Scheme 2.3 [68CJC1057]. The aldol condensation of ethyl acetate with ethyl formate in the presence of sodium ethoxide in ether gave sodium ethyl formylacetate (14) as a white precipitate, from which the corresponding ethoxycarbonyl hydrazone 15 was prepared. The cyclization

of 15 to 16 was found to be a much faster reaction than previously thought. The literature reports that the reaction mixture, after heating to 80°C for one hour, gave a 25% distilled yield of ester 16 [68CJC1057]. We found that a better yield (49% after chromatography) could be obtained by carrying out the reaction at -78°C; the reaction was complete as soon as all the ethoxycarbonyl hydrazone was dissolved (45 minutes to 1.5 hours).



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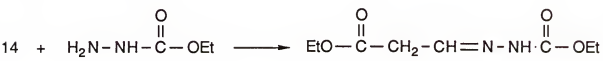

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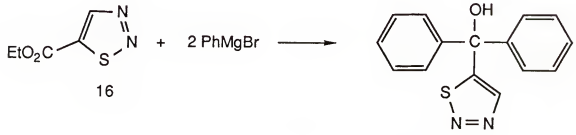
Scheme 2.3

The reaction of ester 16 with two moles of phenyl Grignard reagent was found to be very slow at -78°C. After three hours, a small amount of product was formed but there

were several other products and considerable starting material remained. At higher temperatures much decomposition occurred, as evidenced by a dark brown color, loss of starting material in the TLC and formation of greater amounts of side products. Under optimum conditions, when the temperature was allowed to rise gradually overnight, a 28% yield of carbinol 17 was obtained after purification by flash chromatography.

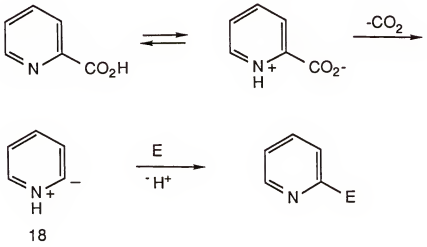


16 17

The 1,2,3-thiadiazole ring is sensitive to strongly basic reagents like alkyl lithiums and Grignard reagents. In addition to the ring opening reaction shown in Scheme 2.1, the ring is also subject to attack by nucleophiles [84MI5]. Apparently, at temperatures low enough to prevent decomposition of the 1,2,3-thiadiazole ring the ester carbonyl group is simply not reactive enough toward the Grignard reagent to obtain the product in good yield.

An alternative approach to the functionalization of the 1,2,3-thiadiazole ring involved decarboxylation of

thiadiazole carboxylic acids in the presence of excess electrophile, by analogy to the Hammick reaction (Scheme 2.4) [39JCS809]. In this scheme, the zwitterionic 2-picolinic acid undergoes decarboxylation to form the intermediate nitrogen ylide **18** [69JA6115] which can add to various electrophiles to form alkylated products. An analogous mechanism can be written for the 1,2,3-thiadiazole-4-carboxylic acid. Both the 4- and 5-(1,2,3)-thiadiazole carboxylic acids undergo decarboxylation on heating to form 1,2,3-thiadiazole [68CJC1057].



18

Scheme 2.4

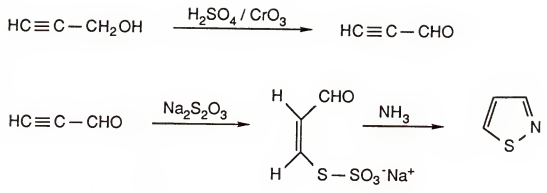
When 1,2,3-thiadiazole-4-carboxylic acid (**11**) was heated in the presence of three equivalents of p-tolualdehyde, the decarboxylation proceeded smoothly at 170-200°C but the ^{1}H nmr spectrum showed that thiadiazole was the sole product.

Upon saponification of ethyl ester 16, 1,2,3-thiadiazole-5-carboxylic acid was obtained in 92% yield. The acid was heated in the presence of three equivalents of p-tolualdehyde. Decarboxylation occurred readily at 120-150°C, but as before, there was no evidence of adduct formation; the ^1H nmr spectrum showed only p-tolualdehyde and 1,2,3-thiadiazole.

Similar results were obtained with sodium 1,2,3-thiadiazole-5-carboxylate, prepared by adding one equivalent of sodium hydride to the carboxylic acid in ethanol followed by evaporation of solvent. The salt was heated in the presence of three equivalents of p-tolualdehyde (heterogeneous mixture), heating to reflux (204°C) for 15 minutes. The reaction mixture was added to D_2O and $CDCl_3$. The nmr of the organic phase showed only p-tolualdehyde while that of the aqueous phase showed only H4 of the carboxylic acid. No decarboxylation occurred (no peak due to H5 of 1,2,3-thiadiazole was visible in the ^1H nmr spectrum).

2.2.2 Compounds Based on Isothiazole

Isothiazole was prepared by the reaction sequence shown in Scheme 2.5. Oxidation of propargyl alcohol gave the corresponding aldehyde in 36% yield. Treatment with sodium thiosulfate gave sodium cis-2-propenal-3-thiosulfate (43%) which was cyclized in liquid ammonia to give isothiazole in 41% yield.



Scheme 2.5

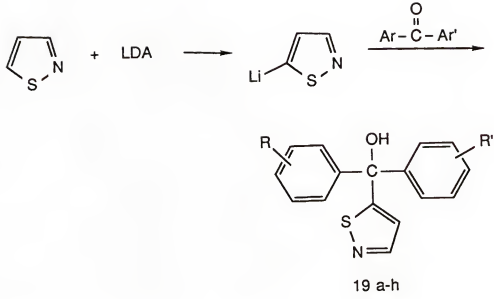
When isothiazole was treated with n-butyllithium at -78°C followed by benzophenone, a mixture of products was obtained. After separation by flash chromatography, a small amount of the desired product **19a** was isolated; its structure was confirmed by ^{1}H nmr and elemental analysis. The major product of the reaction was benzhydrol, identified by melting point, ^{1}H nmr, IR, and TLC. There was also quite a bit of decomposition of the isothiazole ring, as evidenced by a dark brown color, baseline material in the TLC, and aliphatic protons in the nmr of the crude product. Ring opening due to addition of n-butyllithium to the isothiazole ring has been reported previously [64JCS446] and is no doubt at least one cause of the poor yields reported for the carbinol products mentioned above.

In order to avoid addition to the ring, isothiazole was treated with the non-nucleophilic lithiation reagent lithium

diisopropylamide at ~ -70°C, followed by reaction with 4,4'-dichlorobenzophenone (Scheme 2.6). The reaction was followed by TLC; within 30 minutes the benzophenone starting material was virtually gone and a single product spot was observed without any indication of side products or decomposition. Upon workup, product **19b** was isolated in quantitative yield without any purification steps required. It was characterized by melting point, elemental analysis, ^{1}H and ^{13}C nmr.

An even more convenient procedure which gave equally good results was to add the neat isothiazole dropwise to the LDA solution; this obviates the need for two reaction flasks and addition of LDA *via* syringe. A series of compounds (**19c-h**) were prepared by this method. In some cases the reaction was complete within two hours of addition of the benzophenone to 5-lithioisothiazole; in others it was necessary to allow the temperature to rise to 0°C until TLC showed all benzophenone was consumed (see Table 2.1 for details). After work-up, the products were purified by flash chromatography and/or recrystallization. Table 2.1 shows the yields and elemental analyses of the compounds prepared by this method; ^{13}C nmr chemical shifts and assignments are reported in Tables 2.2 and 2.3, ^{1}H nmr data in Table 2.4.

The products were obtained in good to excellent yields. The method represents a considerable improvement in the synthesis of 5-substituted isothiazole compounds, as the yields reported in the literature are usually rather low.



Scheme 2.6

2.2.3 Compounds Based on Thiazole

2.2.3.1 Attempted Grignard reaction with 5-bromothiazole

The reaction sequence shown in Scheme 2.7 illustrates the preparation of 5-bromothiazole. Starting from 2-aminothiazole, treatment with bromine in acetic acid at 65-70°C afforded 2-amino-5-bromothiazole (**20**) in 35% yield. Reductive diazotization then gave 5-bromothiazole (**21**) (55%).

Table 2.1. α,α-Diarylisothiazole-5-methanols (19).

	R	R′	%yield	mp°C	Analysis: Found %C	%H	%N	Molecular Formula	Required: %C	%H	%N
a.	H	H	56[a]	121-23	72.25	5.00	4.89	$C_{16}H_{13}NOS$	71.88	4.90	5.24
b.	4-Cl	4-Cl	100[b]	117-18	57.32	3.25	4.06	$C_{16}H_{11}Cl_2NOS$	57.16	3.30	4.17
c.	4-Cl	H	81[a]	115-16	63.74	3.95	4.58	$C_{16}H_{12}ClNOS$	63.68	4.01	4.64
d.	3,4-diCl	H	85[c]	90.5-91.5	57.34	3.24	4.12	$C_{16}H_{11}Cl_2NOS$	57.16	3.30	4.17
e.	4-OCH_3	H	100[a]	oil[d]	-	-	-	$C_{17}H_{15}NO_2S$	-	-	-
f.	4-CF_3	H	93[a]	119.5-21	60.54	3.58	4.18	$C_{17}H_{12}F_3NOS$	60.89	3.61	4.18
g.	2,4-diCl	H	81[c]	137-38	56.81	3.41	3.95	$C_{16}H_{11}Cl_2NOS$	57.14	3.30	4.17
h.	2-Cl	H	78[c]	109-27	63.36	3.90	4.54	$C_{16}H_{12}ClNOS$	63.68	4.01	4.64

[a]Purified by flash chromatography (microcrystals, except e). [b]No purification required. [c]Purified by recrystallization from 2:1 hexane/ethanol (needles). [d]MW (calculated) 297.0823; found: 297.0824.

Table 2.2. ^{13}C nmr chemical shifts and assignments[a] of α,α-Diaryl-5-isothiazole-methanols (19): Isothiazole Ring Carbons and α-Carbons.

Compound	C3	C4	C5	α-C
a.	157.15	122.74	176.74	78.46
b.	157.22	122.67	176.23	78.71
c.	157.84	123.13	176.99	78.20
d.	157.12	122.44	176.08	78.71
e.	156.88	122.38	177.35	79.10
f.	157.22	122.81	176.08	79.34
g.	156.69	122.86	174.04	79.58
h.	156.64	122.91	174.87	79.88

[a]19c in DMSO; all others in $CDCl_3$.

Table 2.3. ^{13}C nmr chemical shifts and assignments of α,α-Diaryl-isothiazole-5-methanols (19); Aryl Carbons.

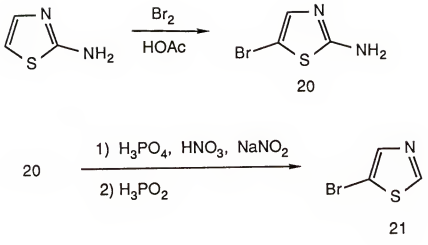
Cmpd	Ring	C1′	C2′	C3′	C4′	C5′	C6′
a.	R=R′=H	145.64	126.98	128.20	a	b	c
b.	R=R′=4-Cl	143.67	128.37	d	134.07	d	d
c.	R=4-Cl	145.31	129.74	126.79	132.25	b	c
	R′=H	145.89	128.00	d	127.57	d	d
d.	R=3,4-diCl	144.45	128.86	132.27	131.88	129.98	126.42
	R′=H	145.77	126.81	128.32	e	b	c
e.	R=4-OCH_3 [f]	137.87	128.22	113.21	158.83	b	c
	R′=H	145.67	126.76	127.93	127.59	b	c
f.	R=4-CF_3 [g]	149.33	125.13 [h]	126.96	130.0 [i]	b	c
	R′=H	144.84	127.30	128.42	e	b	c
g.	R=2,4-diCl	140.16	134.60	130.47	133.05	126.52	130.86
	R′=H	143.67	125.79	128.13	127.83	b	c
h.	R=2-Cl	141.53	132.37	129.49	129.69	126.42	132.25
	R′=H	144.21	125.98	128.03	127.59	b	c

[a]Shoulder on C3′. [b]Equivalent to C3′. [c]Equivalent to C2′. [d]A single large resonance was observed for C2′, 3′, 5′, and 6′. [e]Resonance not observed. [f]OCH_3: δ54.98. [g]CF_3: δ123.92, J_{CF} = 272 Hz. [h]J_{CF} = 3.66 Hz. [i]J_{CF} = 33.0 Hz.

Table 2.4. ^{1}H nmr chemical shifts and assignments of α,α-Diaryl-isothiazole-5-methanols (19).

Compound	H3[a]	H4[a]	Aryl Protons	OH[b]
a.	8.14	6.91	7.29 (s, 10H)	4.51
b.	8.2	6.8	7.2 (s, 8H)	3.5
c.	8.5	7.05	7.45 (s, 9H)	3.3
e.	8.5	7.05	7.2-7.6 (m, 8H)	2.4
g.	8.5	6.9	7.0 (s, 2H) 7.3 (s, 2H) 7.5 (s, 5H)	2.5[c]
h.	8.3	7.0	7.65 (s, 4H) 7.45 (s, 5H)	4.8
f.	8.5	6.95	7.1-7.45 (m, 8H)	4.4
d.	8.3	6.95	7.1-7.4 (m, 9H)	5.25

[a] s, 1H. [b] broad s. [c] OCH_3: δ3.85 (s, 3H).



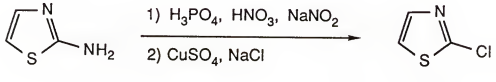
Scheme 2.7

An attempt was made to prepare the Grignard reagent of 5-bromothiazole following the procedure of Kurkjy and Brown [52JA6260] except that 1,2-dibromoethane was used as entrainment reagent instead of ethyl bromide. The reaction was extremely difficult to initiate and did not go very far toward completion. After workup, TLC showed mostly baseline material and unreacted benzophenone with just a faint spot of the expected R_f value. ^1H nmr showed just a trace of heterocyclic protons.

Since the Grignard reaction was unsuccessful, the alternative approach involving protection of the 2-position was undertaken.

2.2.3.2 Protective groups for the 2-position

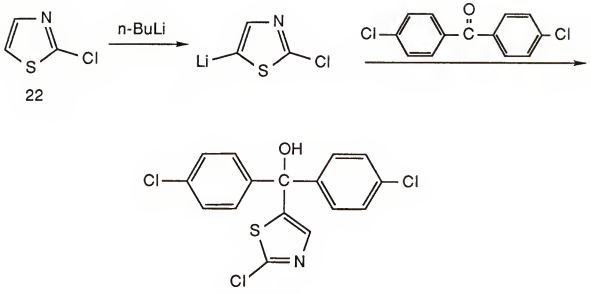
The 2-chloro substituent. Diazotization of 2-aminothiazole followed by treatment with $CuSO_4$/NaCl [45PIA(A)372] gave 2-chlorothiazole (22) in 42% yield.



22

Treatment of 2-chlorothiazole with 1.1 equivalent of n-butyllithium, followed by 4,4'-dichlorobenzophenone gave, after workup, a mixture of carbinol **23** and starting benzophenone (Scheme 2.8). The mixture was purified by flash chromatography to give carbinol **23** in 52% yield. The structure was confirmed by ^1H nmr (Table 2.12), ^{13}C nm (Tables 2.10.and 2.11), and elemental analysis (Table 2.9). A sample was submitted for biological testing.

Dehalogenation of the thiazole ring of **23** with Zn and acetic acid (reflux, 4 hours) was unsuccessful, resulting in what is believed to be an acid catalyzed rearrangement. Under strongly acidic conditions the carbinol should readily form the corresponding tertiary carbocation.



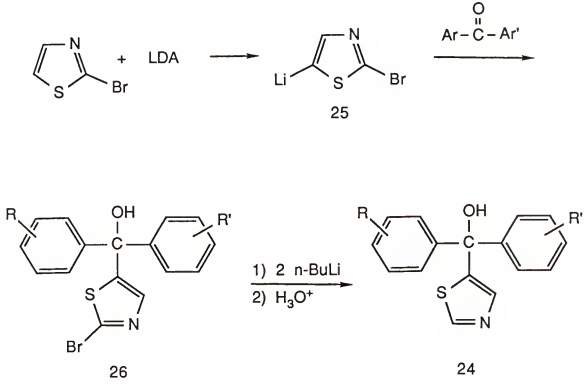
22

23

Scheme 2.8

It has been shown that 2-bromothiazoles undergo halogen-metal interconversion with n-butyllithium [52JA6260]. Although, in general, chlorothiazoles do not undergo this reaction as readily [51OR339], the reaction was attempted with carbinol **23**. Upon treatment of **23** with two equivalents of n-butyllithium at -78°C, followed by quenching with water, a mixture of products was obtained. The nmr spectrum of the crude product mixture showed a signal at δ8.6 indicative of H2 of the thiazole ring [66BSF3524]. Integration suggested that carbinol **24b** comprised about 50-60% of the product mixture, however, the R_f value of **24b** was the same as that of the starting material. This difficulty in purification combined with the rather low yield made it desirable to seek an alternative route to **24**.

The 2-bromo substituent. Since LDA does not cause lithium halogen exchange, we reasoned that 2-bromothiazole could be selectively lithiated at the 5-position using LDA. Thus, the synthesis of carbinols **24** could be carried out as shown in Scheme 2.9 since the 2-bromo substituent exchanges readily with n-butyllithium. Accordingly, 2-bromothiazole was prepared in 65% yield by a procedure analogous to that for 2-chlorothiazole [45PIA(A)372]. Preparation of 2-bromo-5-lithiothiazole (**25**) was accomplished by the controlled addition of 2-bromothiazole to a solution of LDA. Addition of benzophenone followed by a brief period of stirring at -78°C gave, after aqueous workup and purification by flash chromatography, a 56% yield of α,α-diphenyl-2-bromothiazole-5-methanol (**26a**). Its structure was confirmed by ^{1}H and ^{13}C nmr spectroscopy.



Scheme 2.9

The preparation of **25** is somewhat tricky; since the 2-bromo substituent is readily displaced by nucleophiles [79HC(34-1)573] it is essential to keep the concentration of unreacted 2-bromothiazole to a minimum during the addition; otherwise self-condensation occurs and the reagent is destroyed. The 5-lithiation is a very fast reaction, however, so with a reasonable amount of care the 2-bromo-5-lithiothiazole can be prepared. The solution cannot be maintained for any length of time after complete addition without degradation, however; the benzophenone must be added without delay. Once electrophile is added the reaction is quite fast; only about 15 minutes at -78°C is required to give complete reaction.

A series of α,α-diaryl-2-bromothiazole-5-methanols (**26a-f**) were prepared in good yields by this procedure. The results are summarized in Table 2.5. The products thus obtained were yellow to light brown low-melting solids that tended to revert to oils on standing; though not analytically pure they were of sufficient purity for the next reaction in Scheme 2.9. The ^{1}H and ^{13}C nmr spectra of **26a-f** are given in Tables 2.6-2.8. Samples of these compounds were submitted for biological testing.

The α,α-diaryl-2-bromothiazole-5-methanols (**26**) were smoothly converted to the corresponding α,α-diarylthiazole-5-methanols (**24**) by treatment with two equivalents of n-butyllithium in THF at -78°C for 10-15 minutes. After

aqueous workup, yellow to light brown solids or oils were obtained in quantitative yield. The solids were recrystallized from 1:1 hexane/chloroform, while the oils were purified by flash chromatography, giving α,α-diarylthiazole-5-methanols (**24a-f**) in 72-79% yields. The results are summarized in Table 2.9. The structures of **24a-f** were confirmed by ^{1}H and ^{13}C nmr spectroscopy (Tables 2.10-2.12) and elemental analysis. Compounds **24a-f** were submitted for biological screening.

Based on molecular orbital calulations and the results of the initial screening of the compounds thus far described (c.f. Sections 2.3 and 2.4), it was desired to prepare some thiazole compounds with the 2,4-dichloro substitution pattern in the aryl rings, and electron donating groups (e.g. methyl, methoxy, amino) at the 2-position of the thiazole ring.

The 2-bromo compound **26g** appeared to be an ideal intermediate for the preparation of the three compounds shown in Scheme 2.10. Lithium halogen exchange would give the intermediate **27** which could be quenched with H_2O in the normal fashion to give carbinol **24g**, or with methyl iodide to give **28**. Since the bromo substituent is also readily displaced by nucleophiles, treatment of **26g** with sodium methoxide in methanol would give the methoxy compound **29**. Unfortunately, the reaction of 2-bromo-5-lithiothiazole with 2,4-dichlorobenzophenone failed. Addition of one equivalent

Table 2.5. α,α-Diaryl-2-bromothiazole-5-methanols (26).

Compound	R	R'	%yield	mp°C
a.	H	H	62	oil
b.	4-Cl	4-Cl	79	50-85
c.	4-Cl	H	66	48-52
d.	3,4-diCl	H	72	57-70
e.	$4\text{-}OCH_3$	H	71	45-49
f.	$4\text{-}CF_3$	H	72	oil

Table 2.6. ^{13}C nmr chemical shifts and assignments[a] of α,α-Diaryl-2-bromothiazole-methanols (26): Thiazole Ring Carbons and α-Carbons.

Compound	C2	C4	C5	α-C
a.	136.90	140.75	151.18	78.61
b.	137.50	140.75	150.49	78.27
c.	137.14	140.60	150.89	78.07
d.	137.43	140.51	150.50	77.68
e.	136.56	140.41	151.62	78.12
f.	137.43	140.99	150.50	78.32

[a]In $CDCl_3$.

Table 2.7. ^{13}C nmr chemical shifts and assignments of α,α-Diaryl-2-bromothiazole-5-methanols (26); Aryl Carbons.

Cmpd	Ring	C1′	C2′	C3′	C4′	C5′	C6′
a.	R=R′=H	144.99	126.96	128.17	128.03	a	b
b.	R=R′=4-Cl	140.75	128.52	128.32	134.32	a	b
c.	R=4-Cl	143.53	128.27[c]	c	133.88	c	c
	R′=H	144.56	c	c	126.81	c	c
d.	R=3,4-diCl	143.97	129.83	132.37	132.02	128.86	126.42
	R′=H	145.18	126.81	128.32	d	a	b
e.	R=OCH_3[e]	137.24	128.27	113.31	158.93	a	b
	R′=H	145.14	126.76	127.98	127.74	a	b
f.	R=4-CF_3[f]	148.79	126.96	125.27[g]	130.25[h]	a	b
	R′=H	144.36	127.35	128.52	126.66	a	b

[a]Equivalent to C3′. [b]Equivalent to C2′. [c]A single large resonance was observed. [d]Resonance not observed. [e]OCH_3: δ55.02. [f]CF_3: δ123.92; J_{CF} = 272 Hz. [g]J_{CF} = 3.66 Hz. [h]J_{CF} = 33.0 Hz.

Table 2.8. ^{1}H nmr chemical shifts and assignments of α,α-Diaryl-2-bromothiazole-5-methanols (26).

Compound	H4[a]	Aryl Protons	OH[b]
a.	7.0	7.4 (s, 10H)	4.25
b.	7.1	7.4 (s, 8H)	3.5
c.	7.15	7.45 (s, 9H)	3.3
d.	7.05	7.2-7.7 (m, 8H)	4.0
e.	7.05	6.8-7.4 (dd+s, 9H)	3.8[c]
f.	7.0	7.65 (s, 4H) 7.4 (s, 5H)	4.0

[a] s, 1H. [b] broad s. [c] OH plus OCH_3: s, 4H.

Table 2.9. α,α-Diarylthiazole-5-methanols.

	R	R′	R′′	%yield	mp°C	Analysis: Found %C	%H	%N	Molecular Formula	Required: %C	%H	%N
23.	4-Cl	4-Cl	Cl	52[a]	122.5-23.5	51.89	2.60	3.53	$C_{16}H_{10}Cl_3NOS$	51.84	2.72	3.78
24a.	H	H	H	79[b](56)[c]	136-38	71.93	4.95	5.12	$C_{16}H_{13}NOS$	71.88	4.90	5.24
24b.	4-Cl	4-Cl	H	71[b]	146.5-47	56.90	3.22	4.06	$C_{16}H_{11}Cl_2NOS$	57.16	3.30	4.17
24c.	4-Cl	H	H	71[b]	127-28	63.44	3.94	4.52	$C_{16}H_{12}ClNOS$	63.68	4.01	4.64
24d.	3,4-diCl	H	H	78[a]	143-44.5	57.66	3.44	3.97	$C_{16}H_{11}Cl_2NOS$	57.16	3.30	4.17
24e.	$4\text{-}OCH_3$	H	H	72[a]	47-60	68.27	5.29	4.51	$C_{17}H_{15}NO_2S$	68.66	5.08	4.71
24f.	$4\text{-}CF_3$	H	H	81[a]	147-48.5	60.36	3.29	4.10	$C_{17}H_{12}F_3NOS$	60.89	3.61	4.18
24g.	2,4-diCl	H	H	63_a	149-50	57.45	3.13	3.81	$C_{16}H_{11}Cl_2NOS$	57.16	3.30	4.17
28.	2,4-diCl	H	CH_3	100[a]	164-66	58.40	3.58	3.63	$C_{17}H_{13}Cl_2NOS$	58.30	3.74	4.00
33.	2,4-diCl	H	NH_2	61[a]	87-115	54.80	3.62	7.30	$C_{16}H_{12}Cl_2N_2OS$	54.71	3.44	7.98

[a]Purified by flash chromatography (microcrystals). [b]Purified by recrystallization from 2:1 hexane/chloroform (needles). [c]Second recrystallization.

Table 2.10. ^{13}C nmr chemical shifts and assignments[a] of α,α-Diarylthiazole-methanols: Thiazole Ring Carbons and α-Carbons.

Compound	C2	C4	C5	α-C
23.	153.06	139.35	148.63	77.87
24a.	153.81	141.53	-	78.61
24b.	154.76	141.65	147.26	76.59
24c.	153.91	141.33	-	78.27
24d.	154.33	141.51	-	76.74
24e.	153.62	141.48	-	78.21
24f.	154.67	141.65	147.31	77.13
24g.	154.20	142.55	-	79.14
28.	167.51	141.33	144.21	79.14[b]
33.	169.50	137.73	134.46	79.00

[a] **24b, d,** and **f** in DMSO; others in $CDCl_3$. [b] 2-CH_3: δ19.20.

Table 2.11. ^{13}C nmr chemical shifts and assignments of α,α-Diarylthiazole-5-methanols; Aryl Carbons.

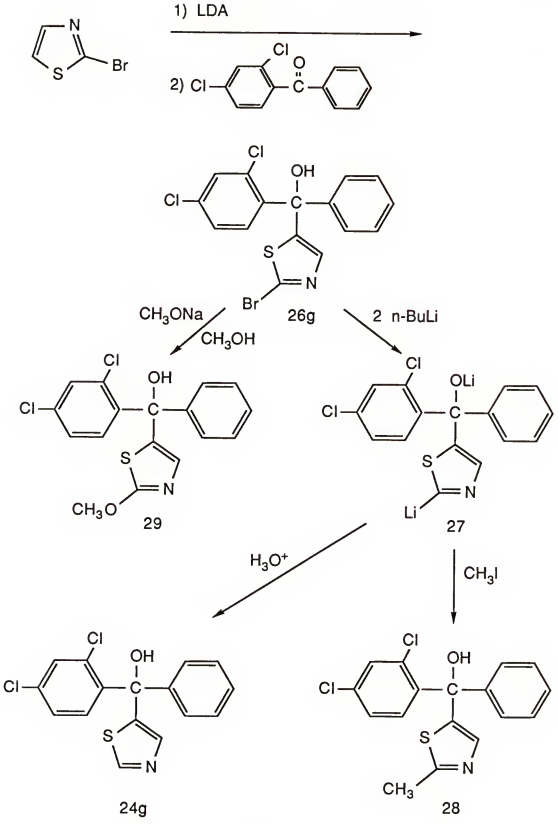
Cmpd	Ring	C1′	C2′	C3′	C4′	C5′	C6′
23.	R=R′=4-diCl	143.01	128.54	128.32	134.36	a	b
24a.	R=R′=H	145.77	127.05	128.13	127.88	a	b
24b.	R=R′=4-Cl	145.31	128.74	127.91	132.25	a	b
24c.	R=4-Cl	144.36	128.47	126.96	133.73	a	b
	R′=H	145.37	128.22	c	128.08	c	c
24d.	R=3,4-diCl	145.60	128.64	130.98	130.35	129.71	127.08
	R′=H	147.50	126.79	127.81	127.47	a	b
24e.	R=4-OCH_3	[d] 138.21	128.42	113.31	159.03	a	b
	R′=H	146.06	128.03	126.96	127.69	a	b
24f.	R=4-CF_3	[e] 151.21	126.84	124.87[f]	127.91[g]	a	b
	R′=H	146.04	127.66	128.01	127.57	a	b
24g.	R=2,4-diCl	141.09	134.95	131.20	133.44	126.86	h
	R′=H	144.01	126.57	128.42	128.22	a	b
28.	R=2,4-diCl	141.19	134.80	131.15	133.44	126.76	131.25
	R′=H	144.01	126.61	128.32	128.13	a	b
33.	R=2,4-diCl	141.04	133.44	130.95	133.15	i	131.29
	R′=H	143.67	126.66	128.08	127.83	a	b

[a]Equivalent to C3′. [b]Equivalent to C2′. [c]A single large resonance was observed for C2′, 3′, 5′ and 6′. [d]OCH_3: δ55.17. [e]CF_3: δ124.2; J_{CF} = 272 Hz. [f]J_{CF} = 3.66 Hz. [g]J_{CF} = 31.7 Hz. [h]C6′and 3′ were superimposed. [i]C5′ and C2′′ were superimposed.

Table 2.12. ^{1}H nmr chemical shifts and assignments of α,α-Diarylthiazole-5-methanols.

Compound	H2[a]	H4	Aryl Protons	OH[b]
23.	-	7.1	7.4 (s, 8H)	3.2
24a.	8.8	c	7.45 (s, 11H)	4.75
24b.	8.9	7.5	7.4 (s, 8H)	3.4
24c.	8.7	c	7.4 (s, 10H)	5.1
24d.	9.1	c	7.2-7.6 (m, 9H)	5.5
24e.	8.8	c	7.3-7.5 (dd+s, 10H)	4.5[d]
24f.	8.8	c	7.65 (s, 4H) 7.45 (s, 6H)	4.0
24g.	8.9	c	6.9-7.6 (m, 9H)	4.55
28.	-	7.1	6.9-7.6 (m, 8H)	4.5[e]
33.	-	6.5	7.3 (s, 2H) 7.5 (s, 6H)	4.8[f]

[a] s, 1H. [b] broad s, 1H. [c] H4 is obscured by the aryl protons. [d] OCH_3: δ3.9, s, 3H. [e] CH_3: δ2.7 (s, 3H). [f] NH_2: δ5.4 (s, 2H).



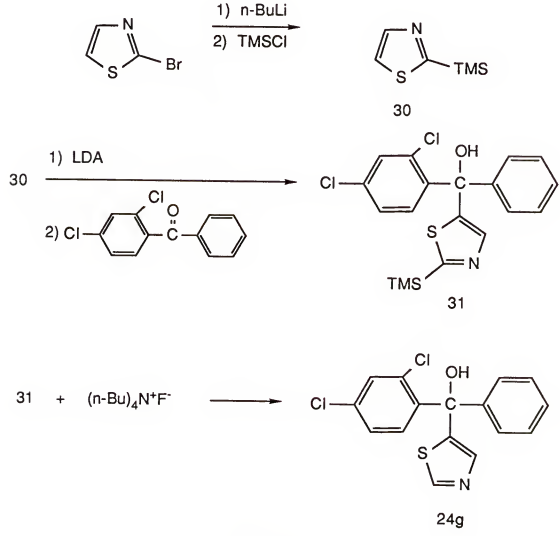
Scheme 2.10

of boron triflouride etherate to the benzophenone prior to addition to **25** did not improve the reaction. The reaction also failed with 2-chlorobenzophenone. It is presumed that the limited stability of the intermediate lithio species (**25**) combined with the increased steric hindrance due to the ortho chloro substituent on the benzophenone prevented these reactions from occurring as expected.

The 2-trimethylsilyl group. An alternative route involving a more stable lithio intermediate was required in order to prepare the desired compounds. The trimethylsilyl group of 2-trimethylsilylthiazole is easily cleaved under mildly acidic conditions but is stable to base [81CC655]; this suggested the reaction sequence shown in Scheme 12.

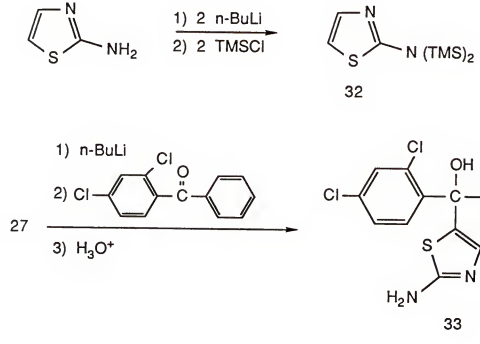
Starting with 2-bromothiazole, lithium-halogen exchange followed in situ by chlorotrimethylsilane gave 2-trimethylsilylthiazole (**30**) in 55% yield. Lithiation of **30** in the 5-position was accomplished by treatment with LDA; addition of 2,4-dichlorobenzophenone then gave the 2-trimethylsilyl-substituted carbinol **31**. The presence of **31** in the crude product mixture was confirmed by the ^{1}H nmr spectrum (large singlet at δ0.35, no H2 peak near δ8.9). However, **31** could not be isolated by flash chromatography as the thiazole ring is easily desilylated by silica gel [81CC655]. Instead, a slight excess of tetrabutylammonium fluoride was added directly to the wet ethereal solution of the crude product. After stirring briefly at room

temperature, the mixture was purified by flash chromatography, giving carbinol **24g** in 63% yield. Treatment of **24g** with LDA followed by methyl iodide gave carbinol **28** in quantitative yield after purification by flash chromatography.



Scheme 2.11

The 2-amino group. The 2-amino compound **33** was prepared starting from the readily available 2-aminothiazole. The amino group was protected as the N,N-bis(trimethylsilyl) derivative [66JCS(C)1706] by treating with two equivalents of n-butyllithium followed by two equivalents of trimethylsilyl chloride (Scheme 2.12). The intermediate **32** was not isolated; it was treated in situ with another equivalent of n-butyllithium followed by 2,4-dichlorobenzophenone. Carbinol **33** was isolated in 61% yield after flash chromatography. Elemental analyses and nmr spectral data for compounds **24g**, **28** and **33** are included in Tables 2.9-2.12. The compounds were submitted for screening as fungicides.



Scheme 2.12

2.2.4 Discussion of NMR Spectra

^{13}C nmr spectra. The ^{13}C chemical shift assignments of heterocyclic ring carbons of carbinols based on the isothiazole and thiazole rings (Tables 2.2, 2.6 and 2.10) were made by comparison to literature values for the parent heterocycles [80MI1, 78CJC46]. Confirming evidence was provided by an APT (attached proton test [81CC150, 82JMR535]). Substitution of C5 of isothiazole and 2-substituted thiazoles by the α,α-diarylcarbinol group caused an average downfield shift of 28 ppm (relative to that of the unsubstituted heterocycle) in the signal for C5. In the unsubstituted thiazole compounds (**24**) (Table 2.10) the signal for C5 was not always observed. The expected peak position is about 147 ppm. In two cases (**24b** and f) a signal was observed (at δ147.26 and 147.31, respectively) which was attributable to C5. In the other spectra the signal for C5 is presumed to coincide with C1'' which is usually observed at δ145-147; in several cases a shoulder can be detected the on C1'' signal. It is certain from the APT that the signal at 153-154 ppm in the thiazole series is C2 and not C5.

The aryl ring carbons (Tables 2.3, 2.7 and 2.11) were assigned by comparing the observed chemical shifts to those calculated by means of substituent parameters [80MI1] using triphenylcarbinol [80JCS(P2)96, 71T735] as a model system.

The APT also aided in these assignments. It was not always possible to make a unique assignment for each ring carbon; in some cases two close peaks may be interchangeable. In a few cases, not every aryl ring carbon was observed; some signals were superimposed on others.

^{1}H nmr spectra. The ^{1}H nmr assignments (Tables 2.4, 2.8 and 2.12) were made based on comparison to literature values for the ring protons in isothiazole [84MI6] and thiazoles [66BSF3524]; the ring protons in the 4-position were shielded by ca. 0.5 ppm compared to the parent heterocycles. For the unsubstituted thiazole compounds (**24**), this shift caused H4 (δ7.9 in the parent ring) to be obscured by the aryl protons.

2.3 Molecular Orbital Calculations

2.3.1 Background

A series of α,α-diphenylmethane heterocyclic compounds based on 5- and 6-membered nitrogen containing heterocycles have been evaluated for fungicidal activity [84MI1]. The data is reproduced in Figure 2.5. The importance of the β-nitrogen for activity is clearly shown by these results; compounds without a β-nitrogen are not active. On the other hand, not every compound with a β-nitrogen is active; for example, the 3-substituted pyridazine compound was totally

inactive while the 4-substituted pyridazine showed only moderate activity. Clearly, all β-nitrogens are not created equal.

There are several factors which influence the biological activity of a compound, and some of these are poorly understood. However, two of the major factors are the steric configuration and the hydrophilic/lipophilic balance. In the compounds shown in Figure 2.5 the "lipophilic backbone" is exactly the same and the steric configuration quite similar, yet there is a great difference in their activity. Regarding the pyridazine compounds, it seems reasonable to suppose that the presence of a second heteroatom (with electronegativity greater than that of carbon) adjacent to the critical β-nitrogen would reduce the electron density at that site, and perhaps the ability of the lone pair electrons to bind with the Fe^{III} of cytochrome P-450. Thus, we reasoned that there may be a correlation between biological activity and electron density at the β-nitrogen, all other things being equal. Electron densities can be calculated by molecular orbital methods. If such a correlation exists, then MO calculations could serve to identify new synthetic targets with a high probability of biological activity and reduce time-consuming syntheses of inactive compounds.

2.3.2 Results and Discussion

An partial geometry optimization was done on the 3-pyridine compound shown in Figure 2.5 using the MNDO program [77JA4899]. The geometries of the pyridine ring and of the phenyl ring were optimized separately; then, for the full molecule, only the bond lengths, angles and dihedral angles about the central carbon remained to be optimized. The results showed there was a considerable net atomic charge (-0.2317) at the β-nitrogen.

The MNDO program has been parameterized to give geometries and heats of formation that agree well with experimental data, while the spectroscopic INDO program [73MI1, 76MI1] is parameterized to give a good wave function. In order to maximize the accuracy of both the geometry and the wave function, the minimum energy geometry obtained *via* MNDO was used as input for a single point INDO calculation. It was necessary, however, to do a complete geometry optimization *via* MNDO first. The results of the full MNDO optimization were almost exactly the same as those obtained from the partial optimization, as far as the net atomic charge on the β-nitrogen was concerned. The INDO program was run using the geometry thus obtained. The Mulliken charges calculated by INDO were quite different; the charge at the β-nitrogen was -0.385 (compared to -0.2318 from MNDO).

Because of the size and complexity of the molecule and the large amount of CPU time required, a model system was tested to see if the calculations could be simplified. Replacing the two phenyl rings by hydrogens significantly reduced the time required for the calculation and, as far as the partial charge at the β-nitrogen was concerned, there was hardly any difference between the Mulliken charges calculated using the full molecule (-0.385) and the model (-0.386). Calculations were run on the active molecules from Figure 2.5 with methyl groups in the place of the diphenylmethyl group. Figure 2.6 shows the calculated values of Mulliken charges at the β-nitrogens.

The values obtained show a reasonable correlation with biological activity values. For example, the 4-substituted pyridazine compound (activity = 4) has a value (-0.213) intermediate between those of the inactive 3-pyridazine compound (-0.060) and the compounds with activity of 8-10 (-0.35 to -0.39). The pyridine compound (activity = 8) has a slightly smaller charge (-0.386) than the pyrimidine compound (-0.393, activity = 10), while the pyrazine compound (activity = 10) has the lowest charge of the three (-0.351). The five-membered rings have slightly larger charges than the six-membered rings though the activity is lower (activity = 6).

While not a statistically significant sample, the results of the calculations do suggest that there is a relationship between biological activity and partial charge

therefore extended to the compounds in our synthetic program. The results of these calculations are shown in Figure 2.7.

The isothiazole and thiazole compounds had values in roughly the same range as the active six-membered ring compounds, but lower than the less active five-membered ring compounds shown in Figure 2.6. The 4-substituted isothiazole compound had a slightly lower charge (-0.330) than the readily prepared 5-substituted compound (-0.345).

The 1,2,3-thiadiazole compounds had far lower charges, and again the position of the methyl group made very little difference in the charges at the nitrogens. The 4-substituted compound was nearly neutral at the β-nitrogen (-0.097). The 5-substituted compound which has two β-nitrogens, had slighlty higher charges; the 2-nitrogen (α to the sulfur) was slightly lower (-0.112) than the 3-nitrogen (-0.151).

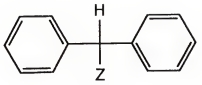
In the case of the thiazole compounds, as expected, the electron withdrawing 2-chloro or 2-bromo substituent reduced the partial charge at the β-nitrogen relative to the unsubstituted ring, though both compounds still had considerable partial charge at the β-nitrogen (-0.342 and -0.350 for the 2-chloro and 2-bromo compounds, respectively) as well as some negative charge at the halo substitutent (-0.201, -0.137). On the other hand, thiazoles substituted with electron releasing groups (amino, methyl and methoxy)

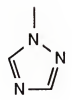
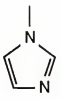
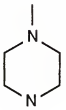
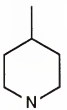
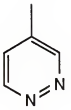
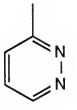
had enhanced partial charges at the β-nitrogen. The values are comparable to those of the active five-membered ring compounds shown in Figure 2.6. In addition to increased electron density at the β-nitrogen, there is almost as large a negative charge at the amino nitrogen and the methoxy oxygen.

2.3.3 Conclusions

The results of these calculations suggest that both the thiazole and isothiazole compounds should exhibit at least moderate biological activity. For the 4-substituted isothiazole compound, it is probably not worthwhile to go through a tedious multistep synthesis to prepare the compound, since it would probably be little different from the 5-substituted compound. The 1,2,3-thiadiazole compounds, which are difficult to prepare, probably would not be highly active in any case.

For the 2-substituted thiazole compounds, other effects make it impossible to predict activity based on these calculations alone. The presence of a 2-substituent on the thiazole ring could well interfere sterically with binding of the β-nitrogen to the heme iron. Additionally, the presence of the substituent could substantially alter the lipophilicity of the compound, which may contribute to or detract from activity. These effects aside, the compounds



Z =						
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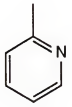
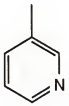
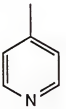
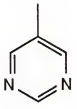
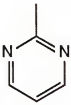
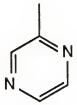
Z =						
Disease Control	0	8	0	10	0	10

Figure 2.5 Control of Bean Powdery Mildew by α,α-Diphenylmethaneheterocyclic Compounds Applied at 400 ppm.

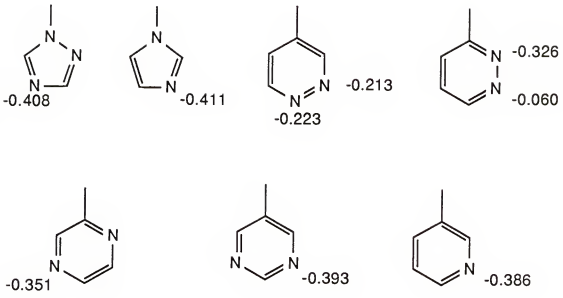


Figure 2.6 Calculated Partial Charges at Selected Heteroatoms: Known Compounds

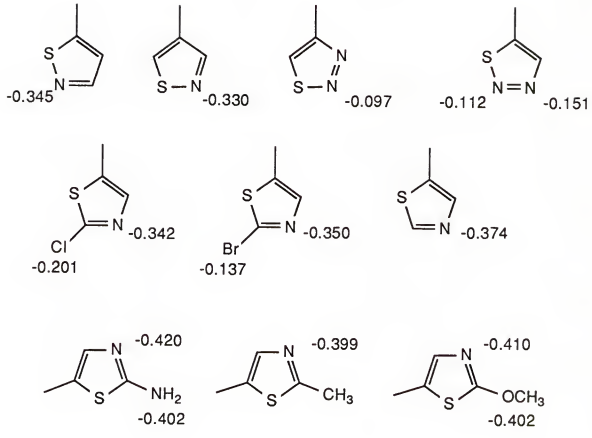


Figure 2.7 Calculated Partial Charges at Selected Heteroatoms: Experimental Compounds

with electron releasing groups should have increased activity over the unsubstituted compounds and those with electron withdrawing substituents. Additionally, a second site of electron density on the molecule may contribute to activity. The results suggested that the preparation of a few examples of thiazole compounds with electron releasing substituents would be worthwhile.

2.4 Results of Biological Testing

2.4.1 Biotest Rationale and Procedure

The biological evaluation of the compounds prepared in this investigation were carried out by Uniroyal Chemical at their Naugatuck Research Center in Naugatuck, Connecticut. The compounds were evaluated for control of a variety of phytopathogenic fungi which were chosen to be representative of the major fungal classes: phycomycetes, ascomycetes, basidiomycetes, deuteromycetes (imperfecti) and mycelia sterilia. The test organisms Fusarium oxysporum, Botrytis cinerea, Alternaria solani, Cercospora arachidicola, Helminthosporium maydis, Sclerotinia sclerotiorum, Sclerotium rolfsii, Phytophthora infestans were used in in vitro tests at concentrations of 500 ppm and lower. In vivo tests were conducted at 1000 ppm and lower with Piricularia oryzae on barley, Erysiphe polygoni on beans, Erysiphe

cichoracearum on cucumber, Erysiphe grammis on barley, and Uromyces phaseoli on beans.

Control of phytopathogenic organisms is conveniently described by an efficacy value defined by

$$\text{efficacy} = \log\left(\frac{\%\ \text{control}}{100}\right) + \log\left(\frac{10^6}{\text{concentration}}\right)$$

where concentration is measured in parts per million. Thus, efficacy provides a single parameter in which large values reflect both high percent control and low concentration; for example, 100% control at 1000 ppm gives efficacy 3.00; 90% control at 50 ppm gives efficacy 4.26. Since control of less than 70% is generally not economically useful, efficacy is arbitrarily redefined as zero if percent control is less than 70% at the test concentration. The most desirable compounds would give 90-100% control against a broad spectrum of organisms at concentrations of 20 ppm or less.

2.4.2 Results and Discussion

The results of biological screening of compounds 19a-d, and g-h, 23, 24a-e, and 26a-e are summarized in Table 2.13. For reasons of space, the table includes only non-zero efficacy values; some of the compounds were moderately active although efficacy was zero. Thus, the discussion

will refer to some data not included in the table. For the purposes of the discussion, moderate activity will be defined as at least 50% control at 500 ppm. (If efficacy were defined at this level of control, it would be 3.0.) Good activity will be defined as 90-100% activity at 100 ppm (efficacy 3.95-4.0), and excellent activity as 90-100% control at $\leq$ 30 ppm (efficacy $\geq$ 4.48).

Compounds with the same lipophilic backbone, but different heterocyclic rings. Compounds **19b**, **23**, **24b**, and **26b** all have the 4,4'-dichloro substitution pattern in the aryl rings, but contain the isothiazole, 2-chlorothiazole, thiazole and 2-bromothiazole rings respectively.

Isothiazole compound **19b** was less active than the corresponding thiazole compound **24b** which showed good activity against bean mildew (erysiphe polygoni on beans) and moderate activity against several other organisms. Compound **26b**, like **24b** except with a 2-bromo substituent on the thiazole ring, showed much less activity. This result was not surprising in view of the expected steric and electronic effects of the 2-bromo substituent. On the other hand, compound **23**, like **26b** except with a 2-chloro substituent, surprisingly showed excellent activity against sclerotinia and botrytis cinerea, as well as moderate activity against other organisms.

In general, the 2-bromothiazole compounds are much less active than the corresponding compounds with an

unsubstituted thiazole ring. Of the four 2-bromothiazole compounds tested, only **26e**, with a 4-methoxy substituent, showed promise; it was highly active against bean mildew and moderately active against several other organisms. The corresponding thiazole compound, **24e**, had a similar level of activity with the addition of some activity against barley mildew (erysiphe graminis on barley) and cucumber mildew (erysiphe cichoracearum on cucmbers).

In comparing the activity of the isothiazole compounds to the thiazole compounds with the same substituents, the only striking feature is that the thiazole compounds usually have excellent activity against bean mildew. Two of the isothiazole compounds (**19a** and **19b**) showed no activity at all against bean mildew, **19c** and **19g** showed good bean mildew activity and **19d** and **19h** were not tested.

Comparison of different ring substituents in compounds with the same heterocyclic ring. Within both the isothiazole series and the thiazole series, varying the substitution pattern on the phenyl rings enhanced activity against some organisms while decreasing activity against others. In the isothiazole series, the best substitution pattern appears to be 2,4-dichloro (**19g**); activity was increased against quite a few organisms compared to the unsubstituted compound and the only decrease in activity was with barley mildew and cucumber mildew. In the thiazole series, 3,4-dichloro substitution (**24d**) gave the best results.

Table 2.13. Results of Biological Screening.

Cmpd	Organism	Conc. of Cmpd.	% control	efficacy
23	Sclerotinia	20 ppm	100	4.70
	"	100	100	4.00
	"	500	100	3.30
	Botrytis cinerea	20	90	4.65
	"	100	100	4.00
	"	500	100	3.30
26b	Sclerotinia	500	80	3.20
26c	Botrytis cinerea	500	90	3.26
26d	Piricularia oryzae	1000	80	2.90
26e	Piricularia oryzae	300	70	3.37
	"	1000	90	2.95
	Bean mildew	30	95	4.50
	"	100	95	3.98
	"	300	95	3.50
	"	1000	100	3.00
	Cucumber mildew	250	80	3.51
24a	Piricularia oryzae	1000	90	2.95
	Bean mildew	30	100	4.52
	"	100	100	4.00
	"	300	100	3.52
	"	1000	90	2.95
	Cucumber mildew	250	80	3.51
24b	Piricularia oryzae	300	96	3.51
	"	1000	90	2.95
	Sclerotinia	500	70	3.15
	"	500	90	3.26
	Bean mildew	100	100	4.00
	"	300	100	3.52
	"	1000	90	2.95
24c	Botrytis cinerea	500	100	3.30
	Phytophthora infestons	500	70	3.15
24d	Piricularia oryzae	1000	80	2.90
	Fusorium oxysporum	500	75	3.18
	Helminthosporum maydis	500	70	3.15
	Phytophthora infestons	500	85	3.23
	Bean mildew	30	100	4.52
	"	100	100	4.00
	"	300	100	3.52
	"	1000	90	2.95
24e	Piricularia oryzae	1000	90	2.95
	Bean mildew	1000	90	2.95
	Barley mildew	250	100	3.60
	Cucumber mildew	250	100	3.60

Table 2.13. Continued

Cmpd	Organism	Conc. of Cmpd.	% control	efficacy
19a	Piricularia oryzae	1000 ppm	100	3.00
	Barley mildew	250	100	3.60
	Cucumber mildew	250	100	3.60
19b	Phytophthora infestons	500	86	3.24
19c	Alternaria soloni	500	70	3.15
	Sclerotinia	500	70	3.15
	"	500	95	3.28
	Bean mildew	100	100	4.00
	"	300	100	3.52
	"	1000	85	2.93
19d	Sclerotium	500	73	3.16
	Sclerotinia	100	70	3.85
19g	Piricularia oryzae	100	80	3.90
	"	300	85	3.45
	"	1000	100	3.00
	Fusorium oxysporum	500	75	3.18
	Helminthosporum maydis	500	70	3.15
	Phytophthoria infestons	500	100	3.30
	Sclerotium	500	80	3.20
	Bean mildew	30	70	4.37
	"	100	90	3.95
	"	300	100	3.52
	"	1000	90	2.95
19h	Alternaria soloni	500	80	3.20
	Botrytis cinerea	500	100	3.30
	Sclerotium	500	100	3.30
	Sclerotinia	20	75	4.57
	"	100	85	3.93
	"	500	100	3.30

2.4.3 Conclusions

Significant levels of fungicidal activity were observed for selected compounds in both *in vitro* and *in vivo* testing although the spectrum of activity can be considered broad only for compounds **19g** and **24d**. The susceptible pathogens are of diverse taxonomy, including phycomycetes, ascomycetes and deuteromycetes.

In both the isothiazole (**19**) and thiazole (**24**) series, halogen substitution enhances activity against most organisms, with the exception of barley mildew and cucumber mildew. The most active compounds from the standpoints of high activity and breadth of spectrum tend to be the unsymmetrical dichloro analogs. This may be due to a requirement for a certain molecular dipole to promote binding at the active site. Unsymmetric substitution is a frequent structural feature in fungicides of the ergosterol biosynthesis inhibitor class. 2,4-Dichloro substitution gave the best results in the isothiazole series and for this reason it was the substitution pattern of choice for the compounds synthesized later in the program.

Introduction of halogens at the 2-position of the thiazole ring appears to diminish activity (bromine, **26**) and narrow the spectrum (chlorine, **23**). This may be an electronic and not a steric effect, however, in light of the excellent activity of the 2-chlorothiazole compound against

two organisms. It is also possible that the decrease in activity of the 2-bromo compounds could be due instead to the ease of displacement of the 2-bromo substituent by nucleophiles (which are abundant in biological media). The 2-chlorothiazoles are much more stable in this regard. Thus, it may be possible to place an electron donating substituent at the 2-position of the thiazole ring without interfering sterically with binding.

In general, the thiazole compounds appear to be a little more active than the corresponding isothiazoles, but in some cases the reverse is true. The thiazoles are more active against bean mildew, but the two types of compounds are similar in their activity against other organisms.

2.5 Summary and Conclusions

A series of compounds of type **8** based on the thiazole, isothiazole and 1,2,3-thiadiazole rings have been prepared and tested for fungicidal activity. During the course of this investigation we have developed an improved method for the functionalization of isothiazole in the 5-position in which we obtained significantly higher yields than those reported previously. We have also developed a general method for the selective functionalization in the 5-position of the otherwise unsubstituted thiazole ring .

Molecular orbital calulations were used to gain insight into the reasons why some compounds are active while other very similar compounds are not. We have found a reasonable correlation between biological activity and electron density at the β-nitrogen for compounds of type 8, and made use of such calculations to predict the activity of the compounds we prepared, and to identify new synthetic targets. Some of the latter were synthesized and submitted for testing.

Although the compounds tested to date are not active enough over a broad enough spectrum to be economically feasible, they do show moderate activity, and these results are in agreement with our predictions. It remains to be seen whether the compounds synthesized in the later portion of the program will have improved activity.

2.6 Experimental

Methods. Melting points were determined on a Hoover capillary melting point apparatus and are uncorrected. ^{1}H nmr spectra were obtained at 60 MHz on a Varian EM 360L nmr spectrometer, with TMS as internal standard. ^{13}C nmr spectra were obtained on a JEOL FX-100 nmr spectrometer at 25 MHz, referenced to solvent ($\delta CDCl_3$ = 77.0, $\delta DMSO\text{-}d_6$ = 39.5). Low and high resolution mass spectra were obtained on an AEI MS30 mass spectrometer. Combustion analyses were performed on a Carlo Erba 1106 elemental analyzer.

All lithiation reactions were carried out in glassware dried overnight at 120°C, assembled hot and placed under an Argon atmosphere using three vacuum/Argon cycles.

Materials. Reagents were obtained from Aldrich with the exception of 2,4-dichlorobenzophenone which was obtained from ICN Biochemicals. Benzophenones were dried in vacuo over P_2O_5 overnight. THF and ether were distilled immediately before use from either CaH_2 or sodium/benzophenone under an Argon atmosphere. Diisopropylamine was distilled from CaH_2 and stored over molecular sieves.

2.6.1 Synthesis of Thiadiazole Derivatives

Ethoxycarbonylhydrazine (9). A two phase mixture of hydrazine monohydrate (8.8g, 0.175 mole) and diethyl carbonate was stirred vigorously under a $CaCl_2$ drying tube until, after 20 minutes, a clear solution was obtained with moderate heat evolution. The reaction mixture was stirred overnight at room temperature. The product was distilled under reduced pressure; yield 11.6g (66%) clear colorless oil, bp 103-6°C/12mmHg (lit. 92-95°C/13mmHg [55OSC(3)404]). The product is reported to be a solid with melting point variously given as 45°C [55OSC(3)404], 51-52°C [14CB2183]. In our hands the product did not solidify and was used as an oil. (A small retainer sample solidified after long standing.) ^{1}H nmr ($CDCl_3$): δ6.8 (s, 1H, NH), δ4.2 (q, 2H, $C\underline{H}_2CH_3$), δ3.9 (s, 2H, NH_2), δ1.3 (t, 3H, $CH_2C\underline{H}_3$).

α-N-Ethoxycarbonylhydrazonopropionic acid (10). Pyruvic acid (6.3g, 0.07 mole) was added dropwise over 15 minutes to a solution of ethoxycarbonylhydrazine (9) (7.4g, 0.07 mole) in toluene (50 ml), keeping the temperature at 30-35°C by means of a cool water bath. The mixture was then stirred overnight at room temperature. The crude product was filtered and dried *in vacuo* at 60°C to yield 12.3g, (99%) yellow crystals, mp 144-57°C. The crude product was refluxed with toluene (200 ml) for three hours. The mixture was allowed to cool overnight, then chilled in an ice bath and filtered. After drying *in vacuo* at 60°C for three hours, 10.4g (84%) light yellow crystals were obtained, mp 152-55°C (lit. mp 157-58°C [55JA5359]). ^{1}H nmr (DMSO): δ10.6 (s, 1H, NH), δ4.24 (q, 2H, $C\underline{H}_2CH_3$), δ2.0 (s, 3H, $N{=}C{-}CH_3$), δ1.23 (t, 3H, $CH_2C\underline{H}_3$).

1,2,3-Thiadiazole-4-carboxylic acid (11). A mixture of α-N-Carbethoxyhydrazonopropionic acid (10) (8.0g, 0.046 mole) and $SOCl_2$ (13.3 ml) was stirred at 0°C overnight, followed by eight hours at room temperature. Gas was evolved and the color gradually darkened to brown. The mixture was cooled to 0°C and filtered, washing with three small portions of ethyl acetate to yield 5.3g (89%) light brown crystals, mp 225°C (dec) (lit. mp 227-28°C [55JA5359]). Recrystallization from ethyl acetate gave 68% recovery of purified 11, mp 226-28°C (dec). ^{1}H nmr (DMSO): δ9.97 (s). ^{13}C nmr (DMSO): δ160.7 (CO_2H), δ155.1 (C4), δ144.9 (C5).

Methyl 1,2,3-thiadiazole-4-carboxylate (12). A solution of 1,2,3-thiadiazole-4-carboxylic acid (11) (2.8g, 21 mmole) in methanol (192 ml) and concentrated H_2SO_4 (8 ml) was heated to reflux overnight, then added to water (200 ml). The pH was adjusted to 7-8 with saturated $NaHCO_3$ and the aqueous phase was extracted with CH_2Cl_2 (3 x 100 ml). The combined organic phases were dried ($MgSO_4$), filtered and evaporated to yield 2.8g (92%) light yellow needles, mp 89.5-90.5°C (lit. mp 89-90°C [65JCS5166]). ^1H nmr ($CDCl_3$): δ9.4 (s, 1H, H5), δ4.1 (s, 3H, CH_3). ^{13}C nmr ($CDCl_3$): δ159.9 (CO_2H), δ154.3 (C4), δ142.6 (C5), δ52.9 (CH_3).

Ethyl formylacetate, sodium salt (14). Sodium hydride (14.4g, 0.6 mole) was suspended in dry ether (300 ml) under an Argon atmosphere. Ethanol (dried over Mg, 35 ml, 0.6 mole) was added dropwise at 0°C with good mechanical stirring; the vigorous evolution of hydrogen was controlled by the rate of addition of ethanol. After standing overnight, the mixture was cooled to -15°C and a mixture of ethyl formate (48 ml, 0.6 mole) and ethyl acetate (59 ml, 0.6 mole) was added dropwise over a period of two hours, keeping the temperature between -15 and -20°C. After standing two hours at -20°C the thick pasty mixture was allowed to slowly warm to room temperature and let stand overnight. The product was filtered, washing thoroughly with three portions of ether. The off-white solid was dried overnight *in vacuo* over P_2O_5: yield 40.9g (59%). ^1H nmr (D_2O): δ8.5 (s, 1H, C(O)H), δ3.8 (q, 2H, $C\underline{H}_2CH_3$), δ0.9 (t, 3H, $CH_2C\underline{H}_3$).

Ethyl formylacetate ethoxycarbonylhydrazone (15). A solution of the sodium salt of ethyl formylacetate (14) (34.5g, 0.25 mole) in water (34 ml) was added to a solution of ethoxycarbonylhydrazine (26g, 0.25 mole) in 4N HCl (72 ml) at 0°C. An oil separated. After stirring 30 minutes at room temperature the mixture was chilled in the freezer with occasional stirring until the oil began to solidify. The solid was filtered and washed twice with water, then dried in vacuo over P_2O_5 overnight; yield 19.7g (39%), mp 59-61°C. A second crop was obtained by cooling the combined filtrate overnight in the refrigerator; yield 2.7g white needles, mp 67-68°C (total yield 44%). A 0.1g sample of the main fraction was recrystallized from water, chilling overnight in the refrigerator; yield 0.1g white needles, mp 69-71°C (no lit. mp given). ^{1}H nmr (CDCl3): δ8.98 (s, 1H, NH), δ7.45 (t, 1H, N=C-H), δ4.0-4.45 (two q, 4H, 2 x $C\underline{H}_2CH_3$), δ3.4 (d, 2H, CH_2), δ1.3 (two t, 6H, 2 x $CH_2C\underline{H}_3$). The crude product was used without further purification.

Ethyl 1,2,3-thiadiazole-5-carboxylate (16). Crude ethyl formylacetate ethoxycarbonylhydrazone (15) was added over a 15-minute period to $SOCl_2$ (40 ml) at -78°C. The reaction mixture was stirred 90 minutes at -78°C; most of the solid dissolved and the solution turned dark brown. It was poured into ice-water (200 ml) and the aqueous phase was extracted with ether (3 x 50 ml). The combined organic phases were washed with H_2O (50 ml), saturated $NaHCO_3$ (2 x 50 ml, pH was 6) and H_2O (50 ml). The ether solution was

dried (Na_2SO_4) and evaporated to yield 15.0g dark brown liquid. The crude product was purified by flash chromatography on 230-400 mesh silica gel with 80/20 petroleum ether/ether. Evaporation of the appropriate fractions gave 6.7g (49%) light yellow liquid (lit. 25% [68CJC1057]). ^{1}H nmr ($CDCl_3$): δ9.25 (s, 1H, H4), δ4.45 (q, 2H, $C\underline{H}_2CH3$), δ1.4 (t, 3H, $CH_2C\underline{H}_3$). ^{13}C nmr ($CDCl_3$): δ158.4 (C=O), δ149.8 (C5), δ146.6 (C4), δ62.7 (CH_2), δ13.8 (CH_3).

1,2,3-Thiadiazole-5-carboxylic acid. A solution of NaOH in methanol (3N, 3.4 ml) was added to ethyl 1,2,3-thiadiazole-5-carboxylate (16) (1.6g, 10 mmole) at 0°C. The mixture was stirred 15 minutes at 0°C, then methanol was removed in vacuo. Water was added to the residue and the solution was acidified to pH 1-2 and continuously extracted with ether for 24 hours. The ether extract was dried (Na_2SO_4), filtered and evaporated to give 1.2g (92%) light yellow solid, mp 105-7°C. A sample (0.87g) was recrystallized from CH_2Cl_2 to yield 0.79g (90%) light tan prisms, mp 107-8°C (lit. mp 103°C [65JCS5166], 104-6°C [68CJC1057]). Found: 27.70%C, 1.40%H, 21.43%N; $C_3H_2N_2O_2S$ requires 27.69%C 1.54%H 21.54%N. ^{1}H nmr (DMSO): δ9.37 (s). ^{13}C nmr (DMSO): δ159.7 (CO_2H), δ150.46 (C5), δ148.7 (C4).

α,α-Diphenyl-(1,2,3)-thiadiazole-5-methanol (17). Phenyl magnesium bromide (3.0M, 2.0 ml, 6.0 mmole) was added dropwise over 15 minutes at -78°C to a solution of ethyl 1,2,3-thiadiazole-5-carboxylate (16) in THF (30 ml). The

reaction mixture was held at -78°C for four hours after whoch the temperature was allowed to slowly increase to room temperature overnight. The reaction mixture was added to saturated NH_4Cl solution (50 ml) and the aqueous phase was extracted with ether (3 x 50 ml). The combined organic phases were dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography (230-400 mesh silica gel, 60/40 petroleum ether/diethyl ether) to yield 0.2g (28%) yellow oil. ^1H nmr ($CDCl_3$): δ8.4 (s, 1H, H4), δ7.4 (s, 10H, aryl), δ4.55 (s, 1H, OH). ^{13}C nmr ($CDCl_3$): δ166.92 (C5), δ146.60 (C4), δ144.79 (C1'), δ128.13 (C3', C5'), δ128.03 (C4'), δ126.61 (C2', C6'), δ78.56 (α-C).

2.6.2 Synthesis of Isothiazole

Propynal. Propargyl alcohol ("practical" grade) was dried over K_2CO_3, then distilled under reduced pressure in the presence of ~1% by weight succinic acid; bp 52-53°C/56 mmHg. A solution of CrO_3 (105g, 1.05 mole) and conc. H_2SO_4 (68 ml) in water (150 ml) was added dropwise under reduced pressure (40 mmHg) to a mixture of propargyl alcohol (60 ml), water (120 ml) and a cooled solution of H_2SO_4 (68 ml) in water (100 ml); the mixture had been cooled to -5°C by means of an ice-salt bath, and the addition was carried out at such a rate that the temperature was maintained between 2 and 10°C; total addition time was about three hours. After

complete addition the pressure was reduced to 15 mmHg and the reaction mixture was allowed to warm to room temperature. The volatile aldehyde product was obtained from the vacuum traps along with considerable water. The aqueous phase was saturated with NaCl and the organic phase was separated to give a pale yellow oil which was used without further purification; yield 19.7g (36%), n_D=1.4155 (lit. n_D=1.4055 [63OSC(4)813]); ^{1}H nmr ($CDCl_3$): δ3.63 (s, 1H, C≡C<u>H</u>), δ9.37 (s, 1H, C(O)<u>H</u>).

<u>Sodium cis-propenal-3-thiosulfate</u>. A solution of sodium thiosulfate pentahydrate (101g, 0.4 mole) in water (120 ml) was added dropwise at -5 to 0°C to a stirred mixture of crude propynal (19.7g, 0.36 mole), acetic acid (21 ml, 0.36 mole), water 979 ml) and acetone (37 ml). After complete addition (about one hour), the mixture was kept at 0°C for 30 minutes, then cold acetone (80 ml) was added. The white precipitate was filtered and dried <u>in vacuo</u> and was used without further purification; yield 25.6g (43%). ^{1}H nmr (D_2O): δ6.5 (dd, 1H, H2), δ7.85 (d, 1H, H3), δ9.65 (bs, 1H, C≡C<u>H</u>).

<u>Isothiazole</u>. Sodium cis-propenal-3-thiosulfate (25.6g, 0.154 mole) was added in portions to liquid ammonia (60 ml) such that the temperature did not exceed -60°C. The mixture was stirred at -78°C for 2.5 hours, then the temperature was allowed to rise and was held at -27°C while the ammonia gradually evaporated. The white solid residue was dissolved

in water (75 ml) and the aqueous phase was extracted with ether (4 x 50 ml). The combined ether phases were dried (Na_2SO_4), filtered and fractionally distilled at atmospheric pressure to give isothiazole as a colorless liquid; yield 5.3g (41%), bp 113-14°C (lit. bp 111-12°C/760mmHg [66CJC1324]); ^1H nmr ($CDCl_3$): δ7.4 (m, 1H, H4), δ8.8 (m, 2H, H2 and H5); ^{13}C nmr ($CDCl_3$): δ156.34 (C3), δ122.72 (C4), δ147.08 (C5). Isothiazole is highly volatile; it was stored over molecular sieves in the refrigerator.

2.6.3 Synthesis of Fungicidal Compounds Based on the Isothiazole Ring

α,α-Diarylisothiazole-5-methanols (19): general synthetic procedure. Lithium diispropylamide was prepared by the dropwise addition of n-butyllithium (2.6M in hexanes, 1.27 ml, 3.3 mmole) to diisopropylamine (0.63 ml, 4.5 mmole) in THF (10 ml) at ≤-70°C. The solution was allowed to warm gradually to 0°C, then cooled again to -78°C. Neat isothiazole (0.22 ml, 3.0 mmole) was added dropwise at such a rate that the temperature did not exceed -70°C. The resulting flocculent white precipitate was stirred at -78°C for two hours. A solution of the appropriately substituted benzophenone (3.0 mmole) in THF (10ml) was added dropwise at ≤-70°C, after which the reaction mixture was stirred at -78°C for two hours or until the reaction was complete as evidenced by the disappearance of the white precipitate and

lack of starting benzophenone in the TLC of a small aliquot of the reaction mixture quenched with NH_4Cl solution. The reaction mixture was then poured into saturated NH_4Cl (50 ml) and extracted with ether (3 x 50 ml). The combined organic phases were dried (Na_2SO_4), filtered and the solvent was evaporated in vacuo. The resulting yellow oil was placed under pump vacuum overnight, then purified by flash chromatography (230-400 mesh silica gel, 60/40 petroleum ether/diethyl ether). If necessary, the products were purified further by recrystallization from 2:1 hexane/ethanol. The yields, melting points and details of purification of compounds **19a-h** prepared by this method are presented in Table 2.1. All the compounds gave satisfactory elemental analyses (Table 2.1) and were characterized by their ^1H (Table 2.4) and ^{13}C (Tables 2.2 and 2.3) nmr spectra.

2.6.4 Synthesis of Thiazole Derivatives

2-Amino-5-bromothiazole (20). 2-Aminothiazole (20g, 0.2 mole) was dissolved in acetic acid (200 ml) and the solution was heated to 65-70°C. A solution of bromine (32g, 0.2 mole) in acetic acid (40 ml) was added at such a rate that the temperature was maintained at 65-70°C. The solution was allowed to cool slowly to room temperature. The solution was decanted from a brown tar which was

deposited on the walls of the flask and evaporated to dryness on the rotary evaporator. The residue was slurried in water (500 ml); an insoluble precipitate was filtered out and the filtrate was made alkaline by the addition of concentrated NH_4OH to pH 8. A light brown, crystalline solid separated which was filtered and dried to give 5-bromo-2-aminothiazole; yield 12.3g (35%), mp 95°C (dec) (lit. mp 93-94°C (dec) [54RTC325]). Found: 20.00%C, 1.51%H, 15.34%N; $C_3H_3BrN_2S$ requires 20.23%C, 1.69%C, 15.73%N. ^1H nmr ($CDCl_3$): δ7.05 (s, 1H, H4), δ5.0 (bs, 2H, NH_2).

5-Bromothiazole (21). A solution of sodium nitrite (7.2g, 0.10 mole) in water (24 ml) was added dropwise at 0 to -5°C to a solution of 2-amino-5-bromothiazole (12g, 0.067 mole) in a mixture of 65% nitric acid (19 ml) and 89% phosphoric acid (96 ml). The resulting thick mixture was stirred at -5°C for 30 minutes. Hypophosphorus acid (36 ml) was added over ~30 minutes at -5°C. Note: this step is dangerous due to vigorous gas evolution in the thick reaction mixture; it must be done very slowly and with very good stirring. The mixture was stirred at -10°C and the temperature was allowed to rise gradually over 18 hours to room temperature. The pH was adjusted to 7-8 by the addition of concentrated sodium hydroxide solution, and the mixture was steam distilled. The organic layer was separated and dried with Na_2SO_4 to yield 6g (54.5%) 5-bromothiazole (21) as a light brown, very dense liquid

which decomposed unless protected from exposure to air. The product was distilled under reduced pressure to give 3.9g (35%) 21, bp 60-63°C/15mmHg (lit. bp 62-63°C/15mmHg [54RTC325]). ^{1}H nmr ($CDCl_3$): δ8.9 (s, 1H, H2), δ7.9 (s, 1H, H4). ^{13}C nmr ($CDCl_3$): δ154.20 (C2), δ144.36 (C4), δ109.12 (C5).

2-Chlorothiazole (22). Concentrated HNO_3 (30 ml) was added dropwise to a solution of 2-aminothiazole (15g, 0.15 mole) in 80% H_3PO_4 (60 ml) at 0°C. The mixture was cooled to -5°C in an ice/salt bath and a solution of sodium nitrite (12g, 0.17 mole) in water (50 ml) was added dropwise over one hour. Stirring was maintained for one hour, then the mixture was slowly added to a solution of $CuSO_4 \cdot 5H_2O$ (39g, 0.156 mole) and sodium chloride (25g, 0.44 mole) in water (100 ml). When the evolution of nitrogen subsided, the mixture was made alkaline by the addition of sodium hydroxide pellets, and subjected to steam distillation. The organic phase of the distillate was separated, ether (50 ml) was added and the solution was dried over sodium sulfate. After filtration and removal of the solvent, crude 2-chlorothiazole was obtained; yield 8.3g (46%). The product was distilled under reduced pressure; initially a colorless oil, the product turned light yellow during the course of the distillation. The yield was 7.5g (42%), bp 49-53°C/22mmHg (lit. bp 45°C/20mmHg [63BSF2504]). ^{1}H nmr ($CDCl_3$): δ7.37 (d, 1H, H5), δ7.7 (d, 1H, H4). ^{13}C nmr ($CDCl_3$): δ151.32 (C2), δ141.09 (C4), δ121.01 (C5). The product decomposed unless protected from air.

2-Bromothiazole. Concentrated HNO_3 (100 ml) was added dropwise to a solution of 2-aminothiazole (50g, 0.5 mole) in 80% H_3PO_4 (200 ml) at 0 to -5°C. A solution of sodium nitrite (40g, 0.58 mole) in water (100 ml) was added dropwise over one hour at 0 to -5°C. After stirring at -5°C for 30 minutes, the mixture was slowly added to a solution of $CuSO_4 \cdot 5H_2O$ (150g, 0.6 mole) and sodium bromide (61.2g, 0.6 mole) in water (400 ml). Evolution of nitrogen continued for several hours; when it subsided, the mixture was neutralized to pH 7-8 by the addition of concentrated sodium hydroxide solution, and subjected to steam distillation. The organic phase of the distillate was separated, dried over calcium chloride pellets, filtered and distilled under reduced pressure. 2-Bromothiazole was obtained as a colorless liquid; yield 53.5g (65%), bp 65-68°C/20mmHg (lit. bp 70.5°C/20mmHg [63BSF1904]). ^1H nmr ($CDCl_3$): δ7.6 (m, 1H, H4), δ7.45 (m, 1H, H5). ^{13}C nmr ($CDCl_3$): δ142.60 (C4), δ135.63 (C2), δ122.86 (C5). The product decomposed unless protected from air; it was stored under Argon over molecular sieves.

2-Trimethylsilylthiazole (30). n-Butyllithium (8.0 ml, 2.5M, 20 mmole) was added dropwise at ≤-75°C to a solution of 2-bromothiazole (1.8 ml, 20 mmole) in ether (80 ml). After stirring one hour at -78°C, chlorotriethylsilane (freshly distilled from CaH_2, 2.8 ml, 22 mmole) was added. The mixture was stirred one hour at -78°C, then was allowed

to slowly warm to room temperature. A tan precipitate was filtered out and the ether was removed in vacuo. A light brown liquid was obtained, yield 4.24g. The crude product was distilled under reduced pressure to give 1.7g (55%) colorless liquid, bp 70-72°C/22mmHg (lit. 55°C/12mmHg [81CC655]). ^{1}H nmr ($CDCl_3$): δ8.25 (d, 1H, H4), δ7.6 (d, 1H, H5), δ0.45 [s, 9H, $(CH_3)_3$]. ^{13}C nmr ($CDCl_3$): δ174.27 (C2), δ145.66 (C4), δ121.27 (C5), δ-1.04 [$(CH_3)_3$].

2.6.5 Synthesis of Fungicidal Compounds Based on the Thiazole Ring

α,α-(4-Chlorophenyl)-2-chlorothiazole-5-methanol (23). A solution of 2-chlorothiazole (3.0g, 25.1 mmole) in ether (25 ml) and a solution of n-butyllithium (2.6M, 10.6 ml, 27.6 mmole) were added simultaneously over a 45 minute period to ether (30 ml) at -78°C. The somewhat brown solution was stirred an additional 2.5 hours with gradual warming to -20°C. 4,4'-Dichlorobenzophenone (12.5g, 50 mmole) in ether (50 ml) was added over 45 minutes. The temperature was allowed to rise to 0°C over one hour, then held at room temperature an additional 30 minutes. Water (100 ml) was added and the aqueous phase was extracted with ether (2 x 100 ml). The combined organic phases were dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was purified by flash chromatography (230-400 mesh silica gel, 80/20 petroleum ether/ether) to give 4.85g (52%)

23, mp 122.5-23.5°C. The elemental analysis is reported in Table 2.9. The ^{1}H nmr spectrum is given in Table 2.12, and the ^{13}C nmr spectrum in Tables 2.10 and 2.11.

α,α-Diaryl-2-bromothiazole-5-methanols (26): general synthetic procedure. Lithium diispropylamide was prepared by the dropwise addition of n-butyllithium (2.6M in hexanes, 3.2 ml, 8.25 mmole) to diisopropylamine (1.59 ml, 11.25 mmole) in THF (20 ml) at ≤-70°C. The solution was allowed to warm gradually to 0°C, then cooled agian to -78°C. A solution of 2-bromothiazole (0.68 ml, 7.5 mmole) in THF (10 ml) was added dropwise without exceeding -75°C, as rapidly as possible at first, then more slowly toward the end of the addition. The total addition time was about 15-20 minutes. The rate of addition was critical; if too much time was taken or the temperature rose too high, considerable decomposition of the starting material occurred as evidenced by the formation of a dark brown color. If all proceeded satisfactorily the reaction mixture at this point was yellow to light brown in color. After stirring 5 minutes at -78°C, a solution of the appropriately substituted benzophenone (7.5 mmole) in THF (10 ml) was added as rapidly as possible without exceeding -70°C. The light brown solution was stirred at -78°C for 15 minutes, then poured into saturated NH_4Cl (75 ml). The aqueous phase was extracted with ether (3 x 50 ml). The combined organic phases were dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The

resulting brown oil was placed under pump vacuum overnight. The crude product was purified by flash chromatography (230-400 mesh silica gel, 80/20 petroleum ether/ether). The products thus obtained (26a-f) are low-melting solids or semi-solids that revert to oils on standing. The yields and melting points of 26a-f are reported in Table 2.5. Their ^{1}H nmr spectra are given in Table 2.8 and their ^{13}C nmr spectra are given in Tables 2.6 and 2.7.

α,α-Diarylthiazole-5-methanols (24): general synthetic procedure. To a solution of α,α-diaryl-2-bromthiazole-5-methanol (26) in THF (5-10ml/mmole) was added dropwise a solution of n-butyllithium (2.6M in hexanes, 2 equivalents plus a 10% excess) at ≤-70°C. The reaction mixture was stirred at -78°C for 15 minutes, then poured into saturated NH_4Cl. The aqueous phase was extracted three times with an equal volume of ether. The combined organic phases were dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude products thus obtained were either solids or oils. The solids were purified further by recrystallization from 2:1 hexane/chloroform, and the oils by flash chromatography (230-400 mesh silica gel, 1:1 petroleum ether/ether). The details of the purification of 24a-f are reported in Table 2.9 along with the yields, melting points and elemental analyses. The products were also characterized by their ^{1}H (Table 2.12) and ^{13}C (Tables 2.10 and 2.11) nmr spectra.

α-(2,4-Dichlorophenyl)-α-phenyl-thiazole-5-methanol (24g). A solution of lithium diisopropylamide was prepared from diisopropylamine (0.84 ml, 6 mmole) and n-butyllithium (2.0 ml, 2.5M, 5 mmole) in THF (10 ml). The LDA solution was added to a solution of 2-trimethylsilylthiazole (30) (0.79g, 5 mmole) in THF (40 ml) at ≤-70°C, then stirred at -78°C for two hours. A white precipitate formed. 2,4-Dichlorobenzophenone (1.26g, 5 mmole) in THF (10 ml) was added and the temperature was slowly allowed to warm to 0°C, at which point the solution was clear. The reaction mixture was poured into saturated NH_4Cl (75 ml) and the aqueous phase was extracted with ether (3 x 50 ml). Tetrabutyl ammonium flouride (5.5ml, 1M, 5.5 mmole) was added to the wet ether extract and the mixture was stirred overnight at room temperature. The ether phase was washed with water (50 ml), dried (Na_2SO_4) and evaporated to yield 2.4g light yellow viscous liquid which was placed under pump vacuum for four hours. A white solid was obtained: yield 1.7g (100%). The crude product was purified by flash chromatography (230-400 mesh silica gel, 70/30 petroleum ether/ether) to give 1.05g (63%) **24g**, mp 149-50°C. The elemental analysis is given in Table 2.9; the ^{13}C nmr spectrum is reported in Tables 2.10-2.11, and the ^{1}H nmr spectrum in Table 2.12.

α-(2,4-Dichlorophenyl)-α-phenyl-2-methylthiazole-5-methanol (28). n-Butyllithium (1.2 ml, 2.5M, 3 mmole) was added to a solution of α-(2,4-dichlorophenyl)-α-phenyl-thiazole-5-methanol (**24g**) (0.50g, 1.5 mmole) in THF (15 ml)

at ≤-75°C. The yellow solution was stirred 20 minutes at -78°C, followed by the addition of iodomethane (0.19 ml, 3 mmole). The reaction mixture was stirred for 45 minutes at -78°C; a white precipitate formed. The mixture was poured into saturated NH_4Cl (25 ml) and extracted with ether (3 x 25 ml). The combined ether phases were dried ($MgSO_4$), filtered and evaporated to give 0.56g yellowish solid. The crude product (0.42g) was purified by flash chromatography (230-400 mesh silica gel, 50/50 petroleum ether/ether) to give 0.40g (95% recovery, 100% overall yield) 28, mp 164-66°C. The elemental analysis is given in Table 2.9; the ^{13}C nmr spectrum is reported in Tables 2.10-2.11, and the ^{1}H nmr spectrum in Table 2.12.

α-(2,4-Dichlorophenyl)-α-phenyl-2-aminothiazole-5-methanol (33). n-Butyllithium (3.2 ml, 2.5M, 8 mmole) was added to a solution of 2-aminothiazole (0.40g, 4 mmole) in THF (30 ml) at ≤-70°C. The slightly cloudy light brown solution was stirred one hour at -78°C, followed by the addition of chlorotrimethylsilane (1.01 ml, 8 mmole). The reaction mixture was allowed to slowly warm to -20°C, then cooled again to -78°C. n-Butyllithium (1.6 ml, 2.5M, 4 mmole) was added at ≤-70°C and the mixture was stirred for 15 minutes at -78°C. 2,4-Dichlorobenzophenone (1.0g, 4 mmole) in THF (10 ml) was added at ≤-65°C. The temperature was slowly allowed to warm to 0°C, then the mixture was stirred at room temperature overnight. The mixture was

poured into saturated NH_4Cl (50 ml) and extracted with ether (3 x 50 ml). The combined ether phases were dried ($MgSO_4$), filtered and evaporated to give 1.7g brown oil. The crude product was purified by flash chromatography (230-400 mesh silica gel) using 50/50 petroleum ether/ethyl acetate (with 1% (v/v) triethyl amine) until all other products were eluted, then pure ethyl acetate to elute the product (R_f = 0.41); yield 0.85g (61%) 33. The melting point (~87-115°C) was difficult to determine due to the incorporation of air in the fluffy solid. The product could not be purified by recrystallization. The elemental analysis is given in Table 2.9; the ^{13}C nmr spectrum is reported in Tables 2.10-2.11, and the ^{1}H nmr spectrum in Table 2.12.

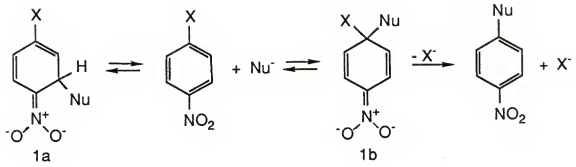
CHAPTER III

AMINATION OF NITROAROMATICS BY VICARIOUS NUCLEOPHILIC SUBSTITUTION

3.1 Introduction

3.1.1 Background

Nucleophilic aromatic substitution of nitroaromatics bearing leaving groups which are capable of leaving as anions (e. g. halides, alkoxides) has long been a standard reaction in organic chemistry. The accepted mechanism involves addition of a nucleophile to form a Meisenheimer complex (1b) in a reversible equilibrium (Scheme 3.1). The Meisenheimer complex can either lose the nucleophile, reverting to starting material, or the leaving group to form the substitution product. Meisenheimer complexes in which the nucleophile attacks a site bearing only a hydrogen atom (1a) form even more readily than 1b; however, since a hydride ion is a poor leaving group, products of substitution of hydrogen are not usually observed unless an external oxidant is present [76RCR454]. Excess nitroarene can serve as the oxidant when the relative oxidation-reduction potentials of the intermediate and the nitroarene are favorable [42JOC98, 76RCR454].

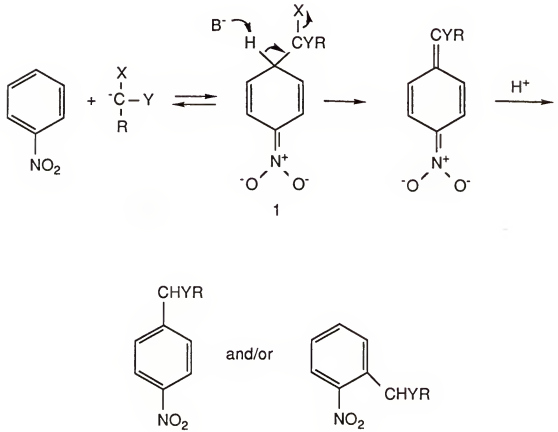


Scheme 3.1

In 1978, Makosza and his co-workers began a systematic study of a new kind of nucleophilic aromatic substitution reaction [78TL3495] (illustrated in Scheme 3.2). He dubbed the reaction "vicarious" nucleophilic substitution of hydrogen, since the leaving group is not hydrogen itself, but a leaving group contained within the incoming nucleophile. Thus, according to Makosza, the hydrogen is removed not as a hydride ion but as a proton in a β-elimination step. Some experimental evidence has been provided in support of this mechanism [83JOC3860], although other studies [84JOC578] suggest that the mechanism may be more complicated.

A structural feature necessary for the success of this reaction is the presence of a carbanion stabilizing group (Y) on the incoming nucleophile. The range of nucleophiles is somewhat limited since this activating group must be one

which prevents the carbon nucleophile from undergoing self-condensation [78TL3495]. The most common activating group used by Makosza is the sulfone group.



Scheme 3.2

Both ortho and para substitution products are usually obtained in the above reaction. The identity and ratio of the products formed were found to be strongly dependent on the ring substituent(s) and could usually be rationalized by a combination of steric and electronic effects [84JOC1488].

The reaction was shown to be applicable to a wide variety of substituted nitroarenes [84JOC1488] and some nitro-substituted heterocycles [84LA8, 84MI7], though the lack of regiospecificity somewhat limits the synthetic utility of the reaction.

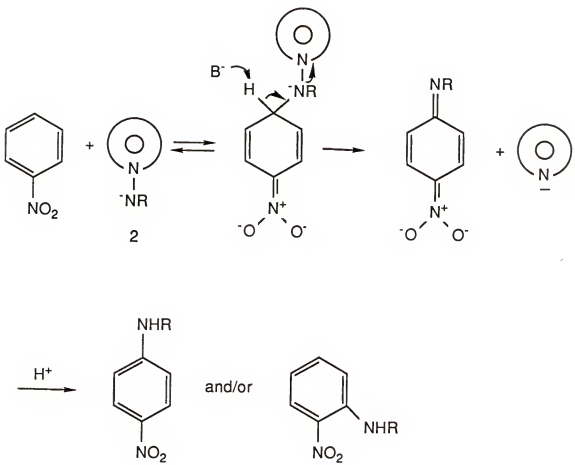
We reasoned that a suitable nitrogen nucleophile with an attached leaving group might allow a similar conversion of nitroarenes into nitroanilines. There are only a few methods reported in the literature for the direct amination of nitrobenzene and these are of limited applicability due to poor yields, and/or inconvenient techniques. Thus, nitrobenzene can be aminated photochemically in liquid ammonia to give 4-nitroaniline in 30% yield [69RTC1339]. With sodamide in liquid ammonia, nitrobenzene undergoes decomposition to give a complex mixture of products [32JCS1254]. When nitrobenzene was refluxed with lithium amide [75CI(L)520], 3-nitroaniline was obtained in only 5% yield, supposedly *via* a benzyne intermediate.

Attempted amination of nitrobenzene with hydroxylamine O-sulfonic acid gave 3-nitroaniline in *ca.* 1% yield [44JA1122]. Some aromatic compounds can be successfully aminated by hydrazoic acid in the presence of $AlCl_3$ or sulfuric acid [64JA1588] but for nitrobenzene the yield was extremely poor (~1%) [44JA1122]. Under basic conditions, 1,3-dinitrobenzene is aminated by NH_2OH [06CB2533] as are 1-[55OSC(3)664] and 2-nitronaphthalene [06CB2533].

Nitrobenzene is aminated by NH_2OH only under unusual conditions. Thus, a German patent claims that nitrobenzene is aminated by NH_2OH in the presence of sulfuric and acetic acids and an $FeSO_4$ catalyst [77GEP2716242], and a U.S. patent reports the amination of arenes by $NH_2OH \cdot HCl$ or $NO \cdot SnCl_2$ in liquid HF [74USP3832364]. Sodium salts of some organic amines form p-substitution products, e.g., sodium or potassium diphenylamide reacts with nitrobenzene in liquid ammonia to give 4-nitrotriphenylamine (up to 45% based on the amide) [42JOC98]; however, an excess of nitrobenzene is required to oxidize the intermediate Meisenheimer complex.

3.1.2 Aim of the Work

As described above, direct amination of nitroarenes suffers from a lack of synthetically useful methods. Vicarious nucleophilic substitution of nitroarenes with a nitrogen nucleophile bearing a leaving group was envisioned as a general method for this purpose. The proposed sequence is shown in Scheme 3.3. The structure of the aminating agent (2) should feature an amino group attached to a suitable leaving group. N-Aminoazoles were considered as excellent candidates for such an aminating agent since the pK_a values of the parent azole rings are rather low. Thus, the azole ring should be a good leaving group in the reaction of Scheme 3.3.



Scheme 3.3

3.2 The Search for an Aminating Agent

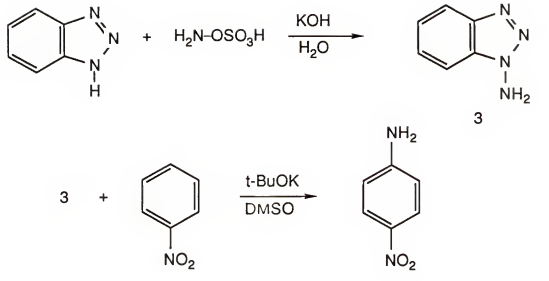
3.2.1 1-Aminobenzotriazole

1-Aminobenzotriazole was first considered as a suitable aminating agent in our proposed sequence (Scheme 3.3).

Since the pK_a of benzotriazole is 8.2 [51JA4360], the conjugate base of benzotriazole was expected to be a good leaving group, thus favoring the β-elimination step.

1-Aminobenzotriazole (3) was prepared by the method of Campbell and Rees (Scheme 3.4) [69JCS(C)742] in 27% yield. In an attempt to achieve the proposed amination sequence, a solution of nitrobenzene and an excess of 1-aminobenzotriazole in DMSO was added dropwise to a solution of two equivalents of potassium t-butoxide in DMSO at 20-25°C. After one hour at room temperature, the reaction was quenched with saturated NH_4Cl. An unidentified light brown solid separated, which melted at 158°C with explosive decomposition. TLC of the organic phase showed the presence of a spot with the characteristic yellow color and R_f value of 4-nitroaniline. The peaks for 4-nitroaniline could be clearly seen in the proton spectrum of the crude product mixture along with those of benzotriazole.

Although the reaction did proceed as expected, the preparation and purification of 1-aminobenzotriazole was not very convenient. Additionally, the R_f value of the product (0.15) was close to that of benzotriazole (0.10), making purification by column chromatography somewhat difficult. For these reasons, this approach was abandoned in favor of another possible aminating agent, benzothiazole-2-sulfenamide (4).

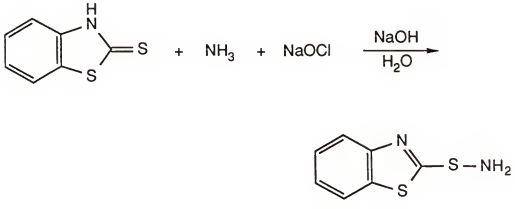


Scheme 3.4

3.2.2 Benzothiazole-2-sulfenamide

Based on similar arguments as for **3** above, we reasoned that the conjugate base of benzothiazole-2-thione would be a good leaving group in the reaction depicted in Scheme 3.3. Accordingly, benzothiazole-2-sulfenamide (4) was considered as a possible aminating agent. It can be conveniently prepared in large scale by the oxidative condensation of benzothiazole-2-thione and ammonia under basic conditions (Scheme 3.5) [49JOC921]. N-Substituted sulfenamides can be prepared in analogous fashion using substituted amines, but this reaction is less satisfactory since it requires excess amine and the product contains impurities which are reported

to accelerate the decomposition of the sulfenamides [61JOC3436]. However, the unsubstituted sulfenamide forms imines with aldehydes and some ketones [57JCS3072], which can be reduced by sodium borohydride to form the N-substituted derivatives [61JOC3436]. The sulfenamide also undergoes transamination in the presence of an excess of a second amine [79MI1] providing a pathway to substituted sulfenamides not readily obtainable by the first method, particularly aromatic derivatives.

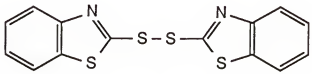


4

Scheme 3.5

Benzothiazole-2-sulfenamide (4) was prepared by the method of Carr, Smith and Alliger [49JOC921] in 81% yield, mp 127-28°C (lit. mp 127-28°C). The crude product contained a small amount of insoluble material, which could be removed by stirring the crude product in ether or chloroform and filtering the insoluble material out. It was observed that the proportion of this insoluble material, believed to be

the disulfide 5 [49JOC921], increased with time, and the product darkened in color. One week after the product was synthesized a 92% recovery of 4 melting at 118-123°C was obtained; after three weeks 83% recovery was obtained, and after 5 weeks only 47%. It has been noted in the literature that the sulfenamides are rather unstable, decomposing in a period of days to months depending on the substitution [49JOC921]. Light, heat and the presence of unreacted starting materials accelerate this decomposition.



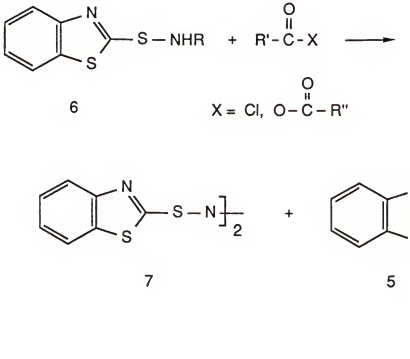
5

In order to achieve the proposed amination, a solution of one equivalent each of sulfenamide 4 and nitrobenzene in DMSO was added dropwise to a solution of two equivalents of potassium t-butoxide in DMSO. After 10 minutes, all the sulfenamide was consumed, as shown by TLC analysis. Only very small amounts of 4-nitroaniline and 2-benzothiazolethione could be observed on TLC. There was a large amount of unreacted nitrobenzene and an unidentified product spot. Neither longer reaction time nor addition of a second equivalent of sulfenamide improved the yield of this reaction.

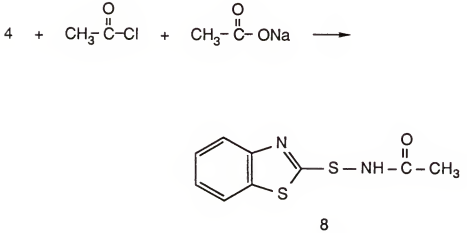
The reaction was tried under a variety of different conditions. No reaction occurred when sodium methoxide was used in methanol, either at room temperature or at reflux (one hour) whereas in neat triethylamine at reflux, a dark brown color developed; TLC analysis showed no 4-nitroaniline product, although the sulfenamide had been partially consumed.

These results suggested that the acidity of the sulfenamide NH_2 group must be very low indeed. We thought that acylation would increase the acidity and so attempted to prepare N-acyl derivatives of 4.

It is well known that sulfenamides in general are unstable under acidic conditions, decomposing to the corresponding disulfides [35JA1517]. The literature reports that attempted acylation of sulfenamides **6** using acid chlorides or anhydrides resulted in the formation of bis-sulfenamide **7** instead, along with varying proportions of disulfide **5** and acylated amine as shown in Scheme 3.6 [77ZOB1096]. The N-acetyl sulfenamide **8** is the only reported example of this class of compound; it was prepared in 30% yield by reaction of sulfenamide **4** with acetyl chloride in the presence of sodium acetate [49JOC921].



Scheme 3.6

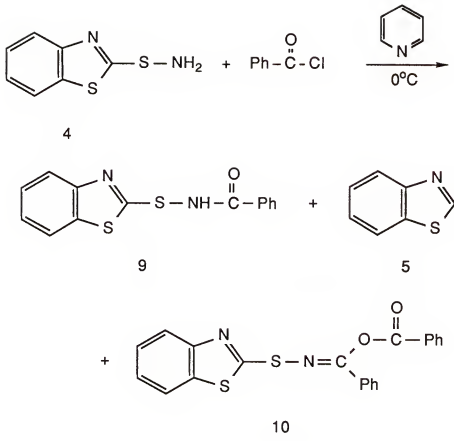


Avoiding acidic conditions, we set out to prepare N-benzoylsulfenamide (**9**). Reaction of **4** with benzoyl chloride under the Schotten-Baumann conditions gave only unreacted starting material. In pyridine at 0°C, the reaction of **4** with one equivalent of benzoyl chloride gave a mixture of products from which the desired N-benzoylsulfenamide (**9**) was obtained in 27% yield. Low resolution mass spectrometry gave a weak molecular ion peak, m/e = 286, together with a fragmentation pattern which was consistent with the structure.

Also obtained in this reaction were the disulfide **5**, (30%), and a product with a molecular ion peak at m/e = 390, identified by X-ray crystallography as **10** (24%), the product of O-acylation of the conjugate base of **9** (Scheme 3.7).

The formation of product **10** can be readily explained by attack of the conjugate base of N-benzoylsulfenamide on a second molecule of benzoyl chloride. This was confirmed by carrying out the reaction with three equivalents of benzoyl chloride; under these conditions **10** was the sole product observed by TLC analysis.

The low yields of amination with sulfenamide **4** and the difficulties associated with the preparation of its N-acyl derivatives directed our attention to an alternative aminating agent, 4-amino-1,2,4-triazole.



Scheme 3.7

3.3 4-Amino-1,2,4-triazole: Amination of 3-Substituted Nitrobenzenes

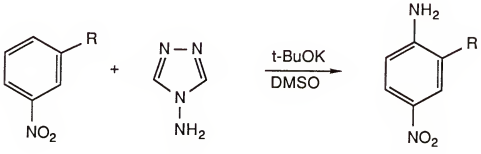
4-Amino-1,2,4-triazole (11) is commercially available and relatively inexpensive. The low pK_a of 1,2,4-triazole (10.26 [84MI7]) indicated that its conjugate base would be a good leaving group in our proposed scheme.

When an equimolar mixture of nitrobenzene and 4-amino-1,2,4-triazole in DMSO was added to a solution of potassium t-butoxide (two equivalents) in DMSO at 24-27°C, immediate formation of an intense yellow-brown color was observed. After 4 hours at room temperature the reaction was quenched with saturated NH_4Cl and extracted with ether. Evaporation of the solvent and purification of the residual yellow solid by flash chromatography (silica gel, 1:1 petroleum ether-ether) gave 4-nitroaniline in 58% yield. The reaction was highly regiospecific, proceeding exclusively in the 4 position with respect to the nitro group; no trace of 2-nitroaniline could be detected on examination of the crude product by TLC or NMR.

This novel amination reaction was then successfully extended to a series of 3-substituted nitrobenzenes to give 2-substituted nitroanilines (12) in fair to good yields (Scheme 3.8). The 2-substituted 4-nitroanilines thus prepared had melting points in accord with literature values. The results are summarized in Table 3.1. The products were characterized by elemental analysis (Table 3.2) as well as ^1H nmr (Table 3.3) and ^{13}C nmr (Table 3.4) spectroscopy.

Several features of this reaction are worthy of discussion. The reaction proceeded satisfactorily in the presence of a variety of substituents, including electron releasing groups such as methyl and methoxy and electron

withdrawing groups such as cyano and halogens. The reaction was also successful in the presence of a 3-carboxylic acid group, even though the intermediate Meisenheimer complex would be a dianion [86S50]. Furthermore, in all cases the 3-substituted nitrobenzenes were aminated in the 4 position with respect to the nitro group. No isomeric derivatives could be detected in the crude product mixtures.



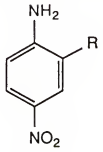
11 12

Scheme 3.8

3.4 Optimization of Reaction Conditions

Our attention was next turned toward optimization of the conditions of the reaction between nitrobenzene and 4-amino-1,2,4-triazole. The reaction was carried out under a variety of different conditions, varying the amounts of 4-amino-1,2,4-triazole and base per mole of nitrobenzene, the order of addition, the base and the solvent.

Table 3.1. 4-Amination of 3-Substituted Nitrobenzenes.



12

	R	% yield	mp(°C)	lit. mp(°C)
a.	H	58	146-8	148-9[a]
b.	CH_3	74	130-30.5	134-5[a]
c.	Cl	91	106.5-7	108[a]
d.	CO_2H	60	279-80(dec)	275-83(dec)[b]
e.	OCH_3	36	138.5-40	139-40[c]
f.	F	47	133-3.5	135-6[d]
g.	I	48	104.5-6	105[e]
h.	CN	22	207-9	210[f]

[a]82MI1. [b]77BCJ338. [c]57ZOB3115. [d]53MI1. [e]01CB3343. [f]46RTC468.

Table 3.2. Elemental Analyses for 4-Nitroanilines (12).

	Found				Required		
	%C	%H	%N	MF	%C	%H	%N
a.	51.95	4.34	19.89	$C_6H_6N_2O_2$	52.17	4.35	20.29
b.	55.01	5.31	18.09	$C_7H_8N_2O_2$	55.26	5.26	18.42
c.	41.69	2.77	15.94	$C_6H_5ClN_2O_2$	41.74	2.90	16.23
d.	45.94	3.16	15.23	$C_7H_6N_2O_4$	46.15	3.30	15.39
e.	49.66	4.79	16.44	$C_7H_8N_2O_3$	50.00	4.76	16.67
f.	46.32	3.20	17.47	$C_6H_5FN_2O_2$	46.15	3.21	17.95
g.	27.19	1.79	10.31	$C_6H_5IN_2O_2$	27.27	1.89	10.61
h.	51.36	3.05	25.30	$C_7H_5N_3O_2$	51.53	3.07	25.77

Table 3.3. ^{1}H nmr Chemical Shifts and Assignments for 4-Nitroanilines (12)[a].

	H2	H3	H5	H6	R	NH_2[b]
a.	6.7 (d,2H)	8.2 (d,2H)	c	d	-	4.4
b.	-	8.0 (m,2H)	c	6.75 (d,1H)	2.2 (s,3H)	6.5
c.	-	8.0-8.4 (m,2H)	c	6.85 (d,1H)	-	4.8
d.	-	8.75 (d,1H)	8.2 (d,2H)	7.0 (d,1H)	8.0 (br s)	3.5
e.	-	7.7-8.0 (m,2H)	c	6.7 (d,1H)	4.0 (s,3H)	4.6
f.	-	8.0 (d,2H)	e	6.9 (d,1H)	-	6.85
g.	-	8.5 (d,1H)	8.1 (dd,1H)	6.9 (d,1H)	-	6.8
h.	-	8.5 (d,1H)	8.2 (dd,1H)	6.95 (s,1H)	-	7.55

[a] **12a,c**, and **e** in $CDCl_3$; others in DMSO. [b] Broad s, 2H. [c] Equivalent to H3. [d] Equivalent to H2. [e] H3 and H5 were superimposed.

Table 3.4. ^{13}C Chemical Shifts and Assignments for 4-Nitroanilines (12).[a]

	C1	C2	C3	C4	C5	C6	R
a.	155.69	112.41	126.35	135.76	b	c	
b.	153.94	120.31	126.16	135.81	123.96	112.27	17.13
c.	151.26	115.58	125.52	135.95	124.50	113.48	
d.	156.23	116.46	128.59	135.17	128.84	108.66	168.26
e.	136.76	145.99	105.59	144.58	110.90	119.67	55.68
f.	144.31[d]	147.92[e]	111.35[f]	134.95[g]	122.26	113.83[h]	
g.	154.96	136.68	125.47	135.07	112.12	79.76	
h.	156.08	92.62	129.32	135.76	130.54	114.95	116.07

[a]In DMSO. [b]Equivalent to C3. [c]Equivalent to C2. [d]J_{CF} = 13.4 Hz. [e]J_{CF} = 240.5 Hz. [f]J_{CF} = 22.0 Hz. [g]J_{CF} = 8.5 Hz. [h]J_{CF} = 4.9 Hz.

Nature of Base. The reaction could also be effected with sodium ethoxide and sodium or potassium hydroxide in DMSO. Sodium and potassium hydroxide have the disadvantage of low solublity in DMSO and therefore the reaction was slower; e. g., with sodium hydroxide, a yield of 57% was obtained after stirring overnight. Sodium ethoxide is soluble but was not a good choice due to impurities present in the commercial material (and the inconvenience of preparation of pure anhydrous material). When sodium hydride was used, at least two other unidentified products were formed (as shown by TLC analysis) in addition to some of the expected product. Overall, potassium t-butoxide gave the best results; it is soluble in DMSO, the reaction proceeds very rapidly and the commercial material was very pure as shown by its ^{1}H nmr spectrum.

Amount of base. Reactions were carried out using one equivalent of 4-amino-1,2,4-triazole with one, two or three equivalents of potassium t-butoxide. With one equivalent of base the yield of 4-nitroaniline was reduced to 17%, while three equivalents of potassium t-butoxide caused a great deal of decomposition of the nitrobenzene as shown by TLC analysis. This is in agreement with Makosza's results [83JOC3860] and shows that excess base should be avoided.

Amount of 4-amino-1,2,4-triazole. Reactions were carried out using two, three and four equivalents of 4-amino-1,2,4-triazole. With two or three equivalents,

unreacted nitrobenzene was present in the crude product mixture; with four equivalents, all nitrobenzene was consumed. However, the yield was not improved. In all cases the yield was in the range of 54-58%.

Order of addition. The original order of addition was modelled after Makosza's procedure whereby a solution of the alkylating (in this case aminating) reagent and the nitrobenzene (one equivalent each) was added dropwise to a solution of two equivalents of base. The reaction was also tried in other ways, e g., a solution of 4-amino-1,2,4-triazole and potassium t-butoxide was added to a solution of nitrobenzene; nitrobenzene was added to a solution of 4-amino-1,2,4-triazole and potassium t-butoxide; a solution of two equivalents of potassium t-butoxide was added to a solution of nitrobenzene and 4-amino-1,2,4-triazole. It made no difference how the reagents were added; the yield was remained in the range of 54-58%. Since the latter procedure was the most convenient it was adopted for all the later reactions.

Solvent. The reaction in DMF using potassium t-butoxide was found to be extremely slow. Following Stahly's procedure, [84JOC578] a solution of 4-amino-1,2,4-triazole and nitrobenzene was added to a solution of potassium t-butoxide in DMF at 0°C. After 3 hours only a small amount of product was formed. After an additional 3 hours at room temperature there was still only a small amount of 4-nitroaniline.

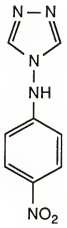
The reaction was successful in 80% t-butanol/20% DMSO, but the crude yield (60%) was no better than in DMSO and the crude product decomposed on standing. The reaction in t-butanol with potassium t-butoxide gave a much lower yield together with a large amount of highly colored decomposition products and unreacted nitrobenzene. In methanol with sodium methoxide there was no reaction even after heating under reflux overnight. TLC showed only the presence of unreacted nitrobenzene. Thus, DMSO is the solvent of choice for these reactions.

For nitrobenzene itself, there appeared to be a maximum yield of 54-58%; none of the other conditions tried resulted in improved yield.

Mass balance. In reactions where unreacted nitrobenzene was recovered, and in reactions where all nitrobenzene was consumed, the amount of product obtained was not sufficient to account for the amount of nitrobenzene consumed. In no case was any other recognizable product isolated from the organic phase; polar decomposition products which remained at the baseline during TLC or column chromatography were sometimes present in varying amounts.

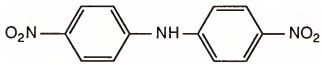
In order to account for the discepancy in the mass balance of nitrobenzene we considered several possibilities. The first was that the first formed Meisenheimer complex was oxidized at the expense of excess nitrobenzene. To the extent that this side reaction occurred, the para

substitution product 13 should be obtained. This was immediately ruled out by comparing the ^{1}H nmr spectra and thin layer chromatograms of some crude product mixtures with those of an authentic sample of 13 obtained by the reaction of 4-amino-1,2,4-triazole with 4-chloronitrobenzene (c.f. Section 3.6.1). No triazole ring protons (δ9.0, s) were visible in the ^{1}H nmr spectra of the crude product mixtures.



13

Another possibility considered was that the substitution product 14 could be formed by reaction of product anion with nitrobenzene.



14

To test this idea, nitrobenzene was treated with an equivalent amount of 4-nitroaniline in the presence of one equivalent of potassium t-butoxide. After one hour a second yellow spot was observed by TLC with R_f value 0.08, overlapping the 4-nitroaniline at R_f 0.15. The reaction was quite slow, however; after two days at room temperature only a 21% yield of **14** was obtained. The isolation of the new product was made simple due to its insolubility in water; it precipitated when the reaction was quenched. Its ^1H nmr spectrum [δ8.3 (d,4H), δ7.45 (d,4H), δ10.1 (broad s, 1H)] was consistent with the structure of **14** and the mp was 210-13°C (literature mp 216-18°C [86BCJ803]). Looking back at the chromatograms of earlier reactions, in some cases there was a faint spot with the correct R_f value for this side product but the amount was not enough to account for the missing nitrobenzene. The formation of **14** is too slow to compete significantly with that of the desired product.

Water soluble side products. The vicarious substitution mechanism requires that 1,2,4-triazole leave as an anion which would then be reprotonated during the aqueous workup. Any excess 4-amino-1,2,4-triazole, which is very water soluble, would also remain in the aqueous phase along with whatever products were derived from the missing nitrobenzene. In order to observe the products remaining in the aqueous phase, the reaction was run on a small scale in DMSO-d_6. After 30 minutes an aliquot was removed and

quenched with one half volume of D_2O. The DMSO/D_2O phase was extracted three times with an equal volume of ether to remove the 4-nitroaniline product, then placed under vacuum to remove residual ether. Examination of the ether phases by TLC showed that all the nitrobenzene had been consumed. The combined ether phases were evaporated and redissolved in DMSO-d_6. The ether phase contained 4-nitroaniline and t-butanol along with some unidentified peaks in the aliphatic region.

The DMSO/D_2O phase contained some of the 4-nitroaniline product along with a complex aromatic region consisting of many small peaks. These must be due to products derived from the missing nitrobenzene, but because of the complexity of the aryl region no useful information could be obtained about their identity.

There was only a very small peak at δ8.5 (the expected position for both 1,2,4-triazole and 4-amino-1,2,4-triazole. This was shown to be due to exchange of ring protons of the 1,2,4-triazole ring with those of the solvent. In the drybox, equivalent amounts of 4-amino-1,2,4-triazole and potassium t-butoxide were dissolved in DMSO-d_6. When the spectrum was taken as quickly as possible, no peaks due to 4-amino-1,2,4-triazole ring protons were observed; the spectrum showed only the t-butyl group and a large OH peak at δ2.6 (residual DMSO plus t-butanol). With potassium hydroxide, again no triazole protons were observed, but an

HOD peak (δ4.2) and a large residual DMSO peak (δ2.5) were present. Both 4-amino-1,2,4-triazole and potassium t-butoxide were stable by themselves in DMSO. The potassium t-butoxide showed only a tiny OH peak and in both cases there was only a very small residual DMSO peak.

In the presence of a single equivalent of base this complete exchange can be rationalized if one postulates a series of equilibria involving the dimsyl anion, which is known to be formed by potassium t-butoxide in DMSO [62JA866]. This was confirmed by repeating the experiment with a catalytic amount of base. Again all the triazole protons disappeared immediately; the ring protons partially reappeared on addition of a small amount of H_2O.

Observation of the reaction by nmr. When one equivalent of nitrobenzene was added to a solution of 4-amino-1,2,4-triazole/potassium t-butoxide in DMSO-d_6 and the spectrum taken immediately, peaks due to product anion were seen along with many small peaks in the aromatic region. There was hardly any change at 5 and 20 minutes, demonstrating that the reaction is quite fast.

When one equivalent of nitrobenzene was added to potassium t-butoxide in DMSO-d_6 there was an immediate development of an intense purple color. The spectrum showed extreme broadening such as might be expected in the presence of a paramagnetic species. More nitrobenzene was added in portions (up to five equivalents) with the same result.

Gradually (over ~20 minutes) the purple color turned to brown and a precipitate appeared. Quenching with D_2O returned the spectrum to normal. The peak due to the t-butyl group was seen along with a complex aromatic region with many small peaks, as before. No nitrobenzene was left. These results and those from the previously mentioned experiments with excess base indicate that nitrobenzene is destroyed by base in a competitive reaction. This explains the fate of the missing nitrobenzene.

The literature reports that the nitrobenzene radical anion is quite stable [68JA347] and its epr spectrum has been observed. It can be formed by chemical [53JPC504] or electrochemical reduction [60JA2671] and by photolysis in basic organic solvents [63TL1333]. It has also been shown to be formed in DMSO in the presence of potassium t-butoxide [64JA1807] and by electron transfer from certain carbanions and nitranions [65MI1, 64JA1807]. Attempts to separate and identify the products derived from these reactions have met with limited success; small amounts of recognizable products were isolated, but often the product mixtures were intractable [70JA4057, 82JA7478]. Given the wide variety of possible coupling, disproportionation and atom abstraction reactions that can occur with radical intermediates, this result is not surprising.

Thus it seems likely that electron transfer reactions are in competition with the amination reaction and that the extent to which these competing reactions take place imposes a limit on the yield which can be obtained.

3.5 4-Alkylamino-1,2,4-triazoles: The formation of Secondary Nitroaniline Products

In order to demonstrate that the vicarious amination reaction is a general one, it was necessary to show that secondary nitroaniline products could be obtained similarly by the reaction of 4-alkylamino-1,2,4-triazoles with nitrobenzenes. Toward this end, a series of 4-alkylamino-1,2,4-triazoles were prepared and their reaction with nitrobenzenes were investigated.

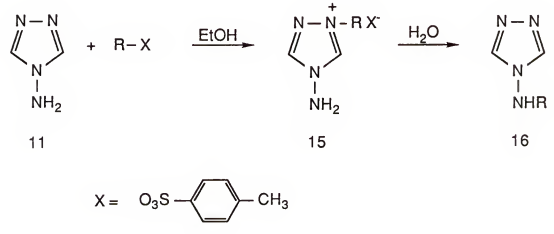
3.5.1 Preparation of 4-alkylamino-1,2,4-triazoles

The literature reports two general methods for the preparation of 4-alkylamino-1,2,4-triazoles. The first method, illustrated in Scheme 3.9, involves the alkylation of 4-amino-1,2,4-triazole in the 1-position to form a quaternary salt 15 which undergoes a base-induced rearrangement to form the N-substituted amine 16 [66MI1, 69JPR9].

Formation of quaternary salts (15). Quaternary salts of type 15 have been prepared with various R groups in yields ranging from 60 to 90% [66MI1].

Compound 15a was prepared by refluxing equimolar quantities of methyl p-toluenesulfonate and 4-amino-1,2,4-triazole for four hours in absolute ethanol. Upon evaporation of the alcohol a quantitative yield of crude

4-amino-3-methyl-1,2,4-triazole p-toluenesulfonate (15a) was obtained. Recrystallization from ethanol/dioxane gave white plates in 85% yield.



Scheme 3.9

Tosylate **15b** was prepared in analogous fashion using ethyl p-toluenesulfonate. The crude product was a slightly yellowish oil which slowly crystallized to an off-white hygroscopic solid, mp 64-70°C. Unlike the methyl analog, the compound could not be purified by recrystallization.

Rearrangement of the quaternary salts. The base catalyzed rearrangement of quaternary salts of type **15** has been reported to give 4-alkylamino-1,2,4-triazoles (**16**) in yields ranging from 52 to 84% [69JPR9]. The quaternary salt, dissolved in a small amount of water, is treated with two equivalents of NaOH and the mixture is heated to 75°C

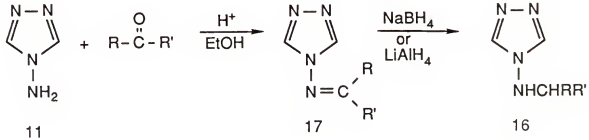
for three hours. Some of the products crystallize from the aqueous phase on cooling; others are water soluble and must be isolated from the aqueous phase by extraction.

Two examples of 4-alkylamino-1,2,4-triazoles (16a and b) were prepared by this reaction sequence. In the case of tosylate 15b, when the reaction was complete, the pH of the solution was adjusted to 12 and it was continuously extracted with ether; this was not very successful in extracting the product. Ethyl acetate and chloroform proved to be better solvents. After prolonged extraction, a 71% yield of crude 4-ethylamino-1,2,4-triazole (16b) was obtained. It was not possible to purify the crude product by recrystallization; the ^{1}H nmr spectrum showed the presence of some impurities.

A more satisfactory procedure was used in the preparation of the methyl derivative 16a. At the end of the heating period, the water was evaporated and the residual solids extracted with chloroform. Evaporation of the solvent gave 4-methylamino-1,2,4-triazole (16b) in 53% yield as a brown oil which was not purified further (the product is reported to decompose on distillation [69JPR9]). ^{1}H nmr showed only very small impurity peaks.

4-Amino-1,2,4-triazole forms imines with aldehydes and ketones [68Tl031, 71MI1, 71MI2]. Schiff bases in general readily undergo reduction by sodium borohydride in methanol to form the corresponding amines in good yields [57JOC1068].

Thus, the second general route to 4-alkylamino-1,2,4-triazoles, illustrated by Scheme 3.10, involves the preparation of an imine 17 by the reaction of 4-amino-1,2,4-triazole with an aldehyde or ketone, followed by reduction with sodium borohydride or lithium aluminum hydride. 4-Benzylamino-1,2,4-triazole has been prepared by the lithium aluminum hydride reduction of imine 17d [66MI1].



11 17 16

Scheme 3.10

Formation of imines (17). A series of imines were prepared by the acid catalyzed reaction of 4-amino-1,2,4-triazole with aldehydes and ketones. Equimolar amounts of 4-amino-1,2,4-triazole and the carbonyl compound were heated under reflux in ethanol in the presence of a drop of concentrated sulfuric acid. Evaporation of the solvent gave excellent yields of imines 17 (Table 3.5).

The reactions with aldehydes were complete within five hours, while reactions with ketones were considerably slower. With acetone, after 5 hours ^{1}H nmr showed that

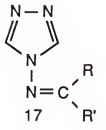
about 25% of unreacted 4-amino-1,2,4-triazole remained. Refluxing overnight in the presence of a large excess of acetone caused little or no further reaction. Some 3A molecular sieves were added to the mixture in order to absorb the water produced in the reaction and force the equilibrium to the side of the product; after 8 hours at reflux, unreacted 4-amino-1,2,4-triazole was no longer visible in the ^1H nmr spectrum. The mixture was filtered and the solvent was evaporated to give **17c** as a slightly yellow oil in 89% yield.

The reaction with cyclohexanone was done in analogous fashion. This reaction was much slower; even after several days under reflux in the presence of molecular sieves, unreacted 4-amino-1,2,4-triazole could still be seen in the ^1H nmr. The product was purified by column chromatography to give **17e** in 87% yield.

Significant spectral details of imines **17** are reported in Table 3.6. Although compounds **17b** [71MI1] and **17c** [71MI2] have been reported in the literature, no data regarding the preparation or physical properties of these compounds were available. Compounds **17e** and **17f** are new compounds.

Reduction of imines to amines. Imine **17d**, dissolved in THF, was treated with an excess of lithium aluminum hydride in a drybox. The reaction was quenched with a small amount of ethyl acetate followed by water. After adjusting the pH

Table 3.5. Preparation of Imines (17).



17

	R	R'	% yield
b.	H	CH_3	100
c.	CH_3	CH_3	89
d.	H	Ph	99
e.	H	$(CH_2)_2CH_3$	87
f.	$-(CH_2)_5-$		87

Table 3.6. ^{13}C and ^{1}H nmr data for 4-alkylideneamino-1,2,4-triazoles (17)[a].

	^{1}H nmr data				^{13}C nmr data		
	Ring[b]	R=H[c]	R≠H	R'	Ring	C=N	R
b.	8.9	8.6(q)	-	2.2 (d,3H)	138.76	161.37	18.62, 16.03
c.	8.4	-	2.1(s,3H)	2.3 (s,3H)	139.04	177.98	25.29, 19.49
d.	9.1	8.5(t)	-	2.4 (q,2H) 1.5 (m,1H) 0.95 (t,3H)	138.92	157.93	132.15, 132.05 129.83, 128.30
e.	8.85	-	2.2-2.8 (m,4H) 1.7-2.0 (bs,6H)		138.72	174.42	34.05, 18.53 13.51
f.	9.1	9.05(s)	7.85 (m,2H), 7.4 (m,3H)		139.74	183.29	34.90, 28.96 26.65, 26.02 24.52, 22.09

[a] In $CDCl_3$. [b] s, 2H. [c] 1H, multiplicity in parentheses.

to 12, the product was isolated by continuous extraction with ether for 24 hours. Evaporation of the dried ether extract gave N-benzyl-4-amino-1,2,4-triazole (**16d**) in 87% yield as a yellow oil which slowly crystallized to a waxy yellow solid.

A more convenient procedure was used for the reduction of the other imines. The crude imine was dissolved in freshly distilled methanol and sodium borohydride powder (one mole per mole of imine) was added portionwise. After the initial gas evolution ceased, the solution was heated to reflux for 15 minutes. The methanol was then evaporated and a minimum amount of 1N NaOH was added to dissolve the residual solids (pH = 12). The small amount of water was then evaporated and the residue was extracted with chloroform. Evaporation of the chloroform solution gave 4-alkylamino-1,2,4-triazoles as white to off-white solids in good to excellent yields. This method proved to be considerably more convenient than the rearrangement route, and where a direct comparison was made (the ethylamino compound **16b**), a higher purity product was obtained in better yield. The preparation of 4-alkylamino-1,2,4-triazoles is summarized in Table 3.7.

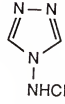
Amines **16c** and **16f** were previously unknown in the literature. They were recrystallized from dioxane/hexane to give white needles with satisfactory elemental analyses (Table 3.7). Amines **16b** and **16e** could not be purified by

recrystallization although they have been reported to be recrystallized from petroleum ether/dioxane [69JPR9]. In our hands they simply oiled out from these and other solvents. The amines have R_f values close to zero in all common solvent systems and thus cannot be purified by chromatography. However, the products were positively identified by high resolution mass spectrometry and/or their ^1H and ^{13}C nmr spectra (Table 3.8) which indicated that they were of sufficient purity to be used in the following amination reactions.

3.5.2 Amination with 4-alkylamino-1,2,4-triazoles

The amination reaction was carried out with the 4-alkylamino-1,2,4-triazoles (16) prepared as described above. The reactions were accomplished by adding a solution of two equivalents of potassium t-butoxide in DMSO to a solution of one equivalent of nitrobenzene and a 20% excess of the amine. After 15-30 minutes the reactions were quenched and the crude products isolated as previously described. The crude products were purified by flash chromatography to give N-substituted 4-nitroanilines (18) in good yields. The results are summarized in Table 3.9. The reactions proceeded in better yields than those with 4-amino-1,2,4-triazole itself, perhaps due to the greater nucleophilicity of the secondary amides.

Table 3.7. Preparation of 4-alkylamino-1,2,4-triazoles (16).



16

	R	R'	% yield[a]	mp°C	Lit. mp°C
a.	H	H	56[b]	oil[c]	-
b.	H	CH_3	71[b], 94[d]	74-77[e]	80[f]
c.	CH_3	CH_3	98	99-101[g]	-
d.	H	Ph	87	102-6	108[f]
e.	H	$(CH_2)_2CH_3$	81	64-70	72[f]
f.	$-(CH_2)_5-$		68[g]	170-72[h]	-

[a]Reduction of imine unless otherwise noted. [b]By rearrangement of the quaternary salts 15; two step yield. [c]MW (calculated) = 98.0592; found: 98.0598. [d]By reduction of the imine: two-step yield. [e]Product of reduction of imine. MW (calculated) = 112.0748; found: 112.0750. [f]69JPR9. [g]Found: 47.54%C, 8.29%H, 45.53%N; $C_5H_{10}N_4$ requires 47.60%C, 7.99%H, 44.41%N. [h]Found: 58.04%C, 8.55%H, 34.37%N; $C_8H_{14}N_4$ requires 57.81%C, 8.43%H, 33.70%N.

Table 3.8. ^{1}H and ^{13}C nmr[a] data for 4-alkylamino-1,2,4-triazoles (16)[a].

	1H nmr data			13C nmr data	
	Ring[b]	NH[c]	R	Ring	R
a.	8.6	6.2(q)	3.05(d,3H)	141.97	40.35
b.	8.55	6.65(bs)	3.2(q,2H) 1.1(t,3H)	143.05	48.17, 12.49
c.	8.5	5.95(d)	3.5(m,1H) 1.1(d,6H)	143.43	52.92, 20.18
d.	8.6	7.1(t)	4.45(d,2H) 7.55(s,5H)	136.81	51.03, 130.67 122.77,122.28 121.60
e.	8.4	5.85(t)	3.15(m,2H) 1.5(m,4H) 0.9(t,3H)	143.04	53.41, 29.38 19.59, 13.55
f.	8.4	5.8(d)	3.0(m,1H) 1.0-1.8(m,10H)	143.53	60.38, 30.65 25.48, 23.83

[a] In $CDCl_3$. [b] s, 2H. [c] 1H; the peaks are fairly broad; coupling with the adjacent alkyl protons is observed (multiplicity indicated in parentheses).

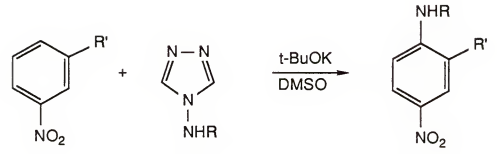
However, the reaction of the crude amine 16d with nitrobenzene gave an unexpected result. The reaction was followed by TLC during addition of base. A deep red-brown color developed and a new spot with the characteristic yellow color was observed at R_f 0.38. Then, between the addition of 1.5 and 2.0 equivalents of base, the product at R_f 0.38 completely disappeared. On quenching with NH_4Cl an insoluble precipitate was formed, which was a mixture of products. Unreacted nitrobenzene was still present.

The reaction was repeated, stopping the addition after only one equivalent of base was added. After workup and purification by flash chromatography, 66% of the starting nitrobenzene was recovered. The product, N-benzyl-4-nitroaniline (18d), was obtained in 17% yield (52% based on nitrobenzene). The cause of the unusual disappearance of the product during the first reaction is unknown, but is probably related to the acidity of the benzyl protons.

The N-substituted 4-nitroaniline products (18) had melting points in accord with literature values, and their ^1H and ^{13}C nmr spectral data are recorded in Tables 3.10 and 3.11 respectively.

Discussion of NMR spectra. In the proton spectra, coupling between the amino and adjacent alkyl protons was observed for the N-substituted 4-nitroanilines (Table 3.10) as well as the 4-(alkylamino)-1,2,4-triazoles (Table 3.8). This phenomenon can be attributed to the reduced basicity of

Table 3.9. Amination with 4-alkylamino-1,2,4-triazoles.



16 18

	R	R'	% yield	mp°C	Lit. mp°C
a.	CH_3	H	79	82-84	81-82[a]
b.	C_2H_5	H	81	94-96	96-98[a]
c.	$CH(CH_3)_2$	H	49	149-51	151-52[a]
d.	CH_2Ph	H	17(52)[b]	145-46	147[c]
e.	$(CH_2)_3CH_3$	H	75	52-54	54-55[d]
f.	cyclo-C_6	H	86	98-100	99-101[e]
g.	C_2H_5	Cl	82	62-64	59.5-60.5[f]
h.	CH_3	I	36	128-30	-
i.	C_2H_5	CH_3	86	95-97	none given[g]
j.	CH_3	CO_2H	98	265-67(dec)	258(dec)[h] 263-64(dec)[i]

[a]69JCS(B)922. [b]Based on nitrobenzene consumed. [c]57JOC1068. [d]78ZOR1654. [e]67CJC195. [f]65NEP6500626. [g]83MI3. [h]79JHC661. [i]48JCS360.

Table 3.10. ^{1}H nmr Chemical Shifts and Assignments for N-Substituted 4-Nitroanilines (18)[a].

	H2	H3	H5	H6	R	NH2a
a.	8.15(d,2H)	6.65(d,2H)	H3	H2	2.85(d,3H)	7.3(q)
b.	8.15(d,2H)	6.75(d,2H)	H3	H2	3.2(m,2H) 1.2(t,3H)	7.35(t)
c.	8.25(d,2H)	6.65(d,2H)	H3	H2	3.8(m,1H) 1.25(d,3H)	4.6(d)
d.	8.1(d,2H)	6.8(d,2H)	H3	H2	4.6(d,2H) 7.45(s,5H)	_[b]
e.	8.0(d,2H)	6.7(d,2H)	H3	H2	3.15(m,2H) 1.5(m,4H) 0.9(t,3H)	6.5(t)
f.	8.05(d,2H)	6.5(d,2H)	H3	H2	3.35(m,1H) 1.1-2.1(m,10H)	4.75(d)
g.		8.2(d,1H)	8.08(dd,1H)	6.62(d,1H)	3.32(m,2H) 1.35(t,3H)	5.02(s)
h.		8.55(d,1H)	8.2(dd,1H)	6.6(d,1H)	2.9(d,3H)	6.4(q)
i.[c]		7.9(d,1H)	8.02(dd,1H)	6.5(d,1H)	3.3(m,2H) 1.35(t,3H)	4.4(s)
j.		8.55(d,1H)	8.05(dd,1H)	6.7(d,1H)	2.9(s,3H)	8.6(s,2H)[d]

[a] **18c** in acetone-d_6, **18a**, **b**, **h**, and **j** in DMSO, others in $CDCl_3$. [b] 1H; coupling with the adjacent alkyl protons is observed (multiplicity indicated in parentheses). [c] Resonance not observed. [d] R′ = CH_3: δ2.1(s,3H). [e] NH_2 and CO_2H are superimposed.

Table 3.11. ^{13}C Chemical Shifts and Assignments for N-Substituted 4-Nitroanilines (18)[a].

	C1	C2	C3	C4	C5	C6	R
a.	155.15	110.27	126.01	135.66	b	c	29.07
b.	154.37	110.51	126.16	135.46	b	c	37.01, 13.86
c.	152.74	111.07	126.37	137.04	b	c	44.10,22.32
d.	152.99	111.32	126.38	137.34	b b	c c	138.41, 128.95 127.88, 127.34
e	153.66	111.78	126.32	137.4	b b	c c	42.98, 30.99 20.03, 13.64
f.	152.64	110.97	126.32	136.85	b	c	51.36, 32.55 24.56, 25.34
g.	148.84	117.50	125.25	137.04	124.76	108.58	38.06, 14.18
h.	153.64	81.37	134.59	136.54	125.76	107.73	30.44
i.[d]	151.57	120.72	125.88	137.09	124.62	107.51	38.06, 14.38
j.[e]	155.30	109.19	128.45	134.54	129.27	111.14	29.56

[a]18a, b, h and j in DMSO, others in $CDCl_3$. [b]Equivalent to C3. [c]Equivalent to C2. [d]R' = CH_3: δ11.65. [e]R' = CO_2H: δ168.46.

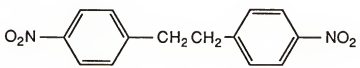
the amino nitrogens, resulting in slow proton exchange [66AJC409]. For the carbon spectra, the aryl ring carbons were assigned by comparing the observed chemical shifts to those calculated by means of substituent parameters [80MI1]. In the 2-substituted 4-nitroaniline series, the observed shifts for C3 and C5 were often quite close. In these cases, ^{13}C - ^{1}H heteronuclear correlation [81JMR501, 83JMR512] allowed the unequivocal assignment of these carbons since the corresponding protons were easily assigned by means of the coupling patterns.

3.6 Amination of Other Nitroaromatic Compounds

3.6.1 Other Nitrobenzenes

Substituents in 2- and 4-positions. When a 4-substituted nitrobenzene is treated with 4-amino-1,2,4-triazole under standard conditions, amination does not occur in the 2-position as might be expected; the reaction takes a different course depending on the substituent. For example, in the reaction with 4-nitrotoluene a mixture of products resulted, from which was isolated a very low yield of 4,4'-dinitrobibenzyl (19), identified by its ^{1}H nmr spectrum [δ8.3 (d, 2H), δ7.3 (d, 2H), δ3.1 (d, 2H)] and melting point: 177-79°C (lit. 179.5-180.5°C [42JOC98]). With 2-nitrotoluene a complex mixture of products was

obtained, with no evidence of any amination in the para position. It is known from the literature that the methyl groups in 2- and 4-nitrotoluenes are acidic and under basic conditions can undergo oxidation to form the corresponding coupling products, 2,2'- or 4,4'-dinitrobibenzyl [62JA4153, 79JOC4705].



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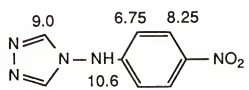
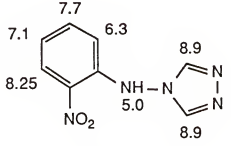
Attempted amination of 4-nitrobiphenyl led only to decomposition of the starting material; no evidence of amination in the 2-position was observed.

In the reaction with 1-chloro-4-nitrobenzene, examination of the ether phase by TLC after quenching the reaction showed no evidence of amination products. On slow evaporation of the ether light yellow needles were obtained, mp 204-206°C. The ^{1}H nmr spectrum of this product was consistent with the product of normal nucleophilic aromatic substitution (13): δ9.0 (s, 2H), δ8.25 (d, 2H), δ6.75 (d, 2H), δ10.6 (broad s).



13

With 1-chloro-2-nitrobenzene, again mostly baseline material was observed by TLC. A very small amount of an unidentified product was isolated by column chromatography. The residue had an nmr spectrum possibly consistent with the 2-substituted product 20 [δ8.9 (s, 2H), δ8.25 (d, 1H), δ7.7 ("t", 1H), δ7.1 ("t", 1H), δ6.3 (d, 1H), δ5.0 (broad, s), though all attempts to isolate this product by recrystallization led only to decomposition.



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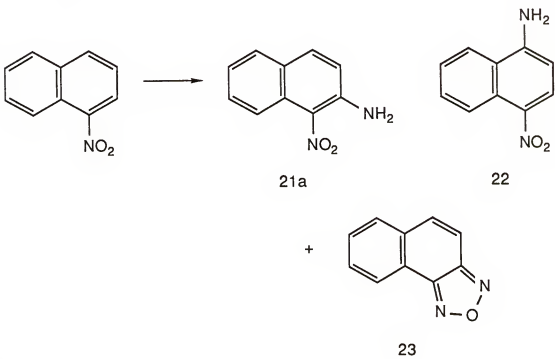
These results are in contrast to Makosza's observations regarding the reaction of substituted nitrobenzenes with halomethyl sulfones; he found that the alkylation reaction proceeded at both 2- and 4-positions, if available [84JOC1488]. Moreover, the vicarious substitution of hydrogen was the exclusive reaction even when leaving groups such as chloro or bromo substituents were present in ortho or para positions; products of normal nucleophilic aromatic substitution were observed only when the very reactive fluorine was present.

3.6.2 Nitronaphthalenes

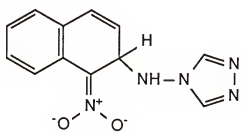
1-Nitronaphthalene. In contrast to the results with nitrobenzenes, the reaction with 1-nitronaphthalene gave a mixture of ortho and para products (Scheme 3.11). 1-Nitro-2-naphthalenamine (21) was obtained in 36% yield, mp 125-26°C (literature 126-27°C [40JGU55]), whereas the para product, 4-nitro-1-naphthalenamine (22), was obtained in 26% yield, mp 190-91°C (lit. 190.5-91.5°C [55OSC(3)664]).



Scheme 3.11

Also obtained in this reaction was a third product, 1,2-naphthofurazane (23), in 30% yield as fluorescent white

needles, mp 78-79°C (lit. 78-79°C [75JOU136]). Thus, substitution at the position ortho to the nitro group is the major reaction with 1-nitronaphthalene, since furazane **23** is presumably formed by the cyclization of ortho product **21** or a related intermediate such as **24**. This is in sharp contrast to the reaction with nitrobenzenes in which reaction occured only at the para position.



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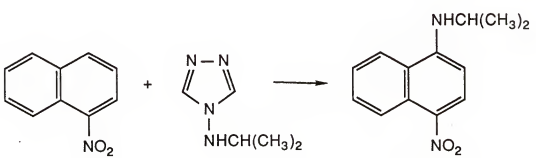
Makosza's results show that the ratio of ortho to para substitution in nitrobenzenes under vicarious nucleophilic substitution conditions depends largely on the steric bulk of the incoming carbanion [84JOC1488]. Para substitution is preferred for all but the smallest reagents, and as the steric bulk increases, the o/p ratio decreases. With tertiary carbanions no ortho substitution is observed, and if the para position is blocked, no reaction occurs. With 1-nitronaphthalene, substitution in the ortho position is generally preferred, and is often the exclusive reaction with smaller carbanions. Para substitution occurs to a

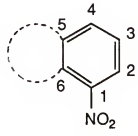
greater extent as the size of the carbanion increases, but considerably more steric bulk can be tolerated by the ortho position of 1-nitronaphthalene than that of nitrobenzene [83S1023, 84JOC1494, 85BSB235].

Molecular orbital calculations using the INDO model [68JCP1807, 73MI1, 76MI1] show that the π-electron density is significantly lower at the ortho position of 1-nitronaphthalene than at the para position, while in nitrobenzene, the π-electron densities at the ortho and para positions are comparable (Table 3.12). These results are consistent with the experimental observations. Thus, in 1-nitronaphthalene electronic factors favor nucleophilic substitution at the ortho position unless high steric demand overcomes the effect, while in nitrobenzene steric effects play the major role in determining the regiochemistry. Apparently, the size of the anion of 4-amino-1,2,4-triazole is large enough to prevent ortho substitution in nitrobenzene, but not in 1-nitronaphthalene. On the other hand, 4-isopropylamino-1,2,4-triazole aminated 1-nitronaphthalene in the 4-position exclusively, giving N-isopropyl-4-nitro-1-naphthalenamine (**22b**) in 98% yield.



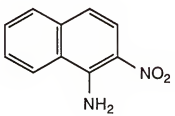
22b

Table 3.12. Π-Electron Densities at Ring Carbons in 1-Nitronaphthalene and Nitrobenene Calculated by the INDO Program.



C	Π-Electron Density	
	1-Nitronaphthalene	Nitrobenzene
1	1.098759	1.090176
2	0.915614	0.955290
3	1.011937	0.994070
4	0.959735	0.951890
5	0.996385	0.994312
6	0.979509	0.955323

2-Nitronaphthalene. When the amination reaction was carried out with 2-nitronaphthalene, 2-nitro-1-naphthalenamine (25) was obtained in 70% yield as orange-brown needles, mp 140-1°C (literature 144°C [31RTC37]).



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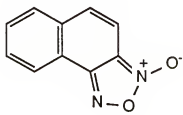

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There was no evidence of the formation of any furazane product in this reaction. This result tends to rule out the proposed cyclization of nitronaphthalenamine 21 as the source of furazane 23 since the isomeric nitronaphthalenamine 25 should have given the identical product under the same reaction conditions. Both 1-nitro-2-naphthalenamine and 2-nitro-1-naphthalenamine have been shown to undergo cyclization upon treatment with NaOCl to form 1,2-naphthofuroxane 26 [17JCS612]. The furazane 23 can be formed by cyclization of either isomer of ortho nitrosonaphthalenamine (using NaOCl) or by dehydration of 1,2-naphthoquinone dioxime [75JOU136]. The possibility that furoxane 26 was formed first and was then reduced to furazane 23 was also ruled out since the latter was not

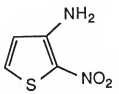
produced in the reaction with 2-nitronaphthalene. Alternatively, the nitro group might have been reduced to a nitroso group, followed by cyclization to the furazan 23. There is some precedent in the literature for such a transformation of 1-nitronaphthalene [70MI1].

3.6.3 Heterocyclic Substrates

The reaction of 11 with pyridine failed both at room temperature and higher (150°C). With pyridine N-oxide, again no amination products were isolated. These results are not surprising in view of the fact that Makosza's reaction also failed for pyridine and its N-oxide [84LA8], although it was successful with nitropyridines [84LA8] as well as nitrothiophenes and N-methyl-nitropyrroles, and marginally successful with nitrofuran [84MI8].

In the present study, the vicarious amination reaction was carried out with 2-nitrothiophene (the staring material as obtained from Aldrich contains 15% of 3-nitrothiophene). 2-Nitro-3-thiophenamine (27) was obtained in 15% yield as yellow-brown needles, mp 158-59°C (literature 158-59°C [76BSF151]). None of the isomeric product **28** was obtained. It is perhaps not surprising that **28** was not formed in light of the fact that Makosza's reaction between 2-nitrothiophene and chloromethylphenylsulfone gave only the 3-substituted product. On the other hand, the same reaction with

3-nitrothiophene gave 2-substituted product in good yield. Product 29, which might have been expected from reaction of 11 with the 15% of 3-nitrothiophene present in the starting material, was likewise not observed, probably for steric reasons as discussed above. The reaction was accompanied by much decomposition as evidenced by the formation of an insoluble black precipitate on quenching.



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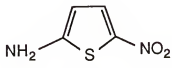

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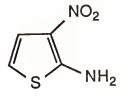

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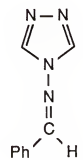
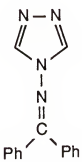
3.6.4 Other substrates

The amination reaction was also attempted with some aromatic substrates lacking activation by a nitro group. In the reaction with benzaldehyde, two products were isolated in low yields (~10%). Simple imine formation was immediately ruled out by comparison of the ^{1}H nmr spectra to that of an authentic sample of 17c (c. f. Section 3.5.1). High resolution mass spectrometry gave the molecular weights of the two products as 275 and 273, corresponding to molecular formulae of $C_{16}H_{13}N_5$ and $C_{16}H_{11}N_5$, respectively. The formulae require the condensation of two molecules of

benzaldehyde with loss of both oxygen atoms and require the participation of two molecules of 4-amino-1,2,4-triazole, with loss of one triazole ring. Due to the very limited amount of sample, the structures of these products were not fully elucidated.



17c



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The reaction of 11 with ethyl benzoate was exothermic but unlike most of the other reactions no color development was observed. No products were obtained on extraction of the aqueous phase (pH 7-8) after quenching. The aqueous phase was then acidified to pH 1 and re-extracted. Just a trace of unidentified material was recovered.

With benzophenone, a complex mixture of products was formed. On separation by flash chromatography, only very small amounts of unidentified products were isolated. There was no evidence of formation of the imine 30.

Benzaldehyde, benzophenone and ethyl benzoate have all been reported in the literature to react in DMSO in the presence of base to form products derived from addition of the dimsyl anion to the carbonyl group [62JA866, 63JA3410].

3.7 Conclusions

In this investigation, we have demonstrated that direct amination of nitroaromatics, a transformation which has been difficult in the past, can be accomplished conveniently and in good yields by a vicarious substitution sequence using 4-amino-1,2,4-triazole. The reaction is highly regiospecific, affording 4-nitroanilines exclusively, and is compatible with a variety of other substituents on the aromatic ring. Additionally, N-substituted 4-nitroanilines can be readily prepared using 4-alkylamino-1,2,4-triazoles as the aminating agent. The latter were easily prepared by reductive condensation of 4-amino-1,2,4-triazole and the corresponding aldehydes or ketones in high yield and require no purification before use in the amination reaction. The reaction was found to be general for nitrosubstituted aromatics.

3.8 Experimental

Methods. Melting points were determined on a Hoover capillary melting point apparatus and are uncorrected. ^{1}H nmr spectra were obtained at 60 MHz on a Varian EM 360L nmr spectrometer, with TMS as internal standard. ^{13}C nmr spectra were obtained on a JEOL FX-100 nmr spectrometer at 25 MHz, referenced to solvent ($\delta CDCl_3$ = 77.0, $\delta DMSO\text{-}d_6$ = 39.5). Two dimensional nmr spectra were obtained on a

Varian XL-200 nmr spectrometer at 200 MHz for proton and 50 MHz for carbon. High resolution mass spectra were obtained on an AEI MS30 mass spectrometer. Combustion analyses were performed on a Carlo Erba 1106 elemental analyzer. The X-ray crystallographic analysis was performed on a Nicolet R3m Diffractometer.

Materials. Reagents were obtained from Aldrich with the exception of 4-amino-1,2,4-triazole which was the generous gift of Reilly Tar and Chemical Co. Nitrobenzene was distilled from P_2O_5 and stored over molecular sieves. 4-Amino-1,2,4-triazole and substituted nitrobenzenes were dried *in vacuo* over P_2O_5 immediately before use, with the exception of 4-methylamino-1,2,4-triazole and 3-nitrotoluene which were dried over molecular sieves. Potassium *t*-butoxide was stored and weighed in a dry-box. DMSO was obtained in an Aldrich Sure-Seal bottle and was transferred *via* syringe under inert atmosphere (N_2 or Ar). All amination reactions were carried out under dry N_2 or Argon.

3.8.1 Preparation of Proposed Aminating Agents

1-Aminobenzotriazole (3). Benzotriazole (11.9g, 0.1 mole) was dissolved in a solution of KOH (28g, 0.5 mole) in water (100 ml). Solid hydroxylamine-O-sulfonic acid (22.6g, 0.2 mole) was added in portions at 70-75°C over one hour. After one more hour at 70-75°C, the mixture was cooled and

filtered. The filtrate was extracted with ether (3 x 100 ml). The solid was washed well with ether and the combined ether phases were dried over $MgSO_4$. Evaporation of the solvent gave a mixture of 1- and 2-aminobenzotriazole as a light brown oil (7g, 52%). The crude product was purified by flash chromatography (230-400 mesh slica gel, 60/40 petroleum ether/dietyl ether) to give 3.6g (27%) 1-aminobenzotriazole (3) as a light yellow oil and 0.45g (3%) 2-aminobenzotriazole as an off-white solid. ^1H nmr of 3 ($CDCL_3$): δ8.0-7.0 (m, 4H), δ5.9 (s, 2H).

The crude 1-aminobenzotriazole could not be recrystallized from benzene/petroleum as per the literature procedure (lit mp 84°C [69JCS(C)742]). The only result was darkening of the oily product. The product also darkened on standing at room temperature.

1-Aminobenzotriazole was purified a second time by flash chromatography and the light yellow oil (1.2g) thus obtained was used without further purification.

Reaction of 1-aminobenzotriazole with nitrobenzene. A solution of 1-aminobenzotriazole (0.54g, 4 mmole) and nitrobenzene (0.1 ml, 1 mmole) in DMSO (5 ml) was added dropwise to a solution of potassium t-butoxide (0.22g, 2 mmole) in DMSO (5 ml) at 20-25°C. After stirring one hour at room temperature, TLC showed the presence of a spot with the characteristic yellow color and R_f value (0.15, 1:1 petroleum ether/ether) of 4-nitroaniline. The reaction was

quenched in saturated NH_4Cl, and a solid separated. The solid was filtered and dried and was recrystallized from 1:1 aqueous ethanol to give a light brown solid which melted at 158°C with explosive decomposition. ^1H nmr was not helpful in determining the structure of this product.

The aqueous phase was extracted with CH_2Cl_2, dried and evaporated to give a brown oil (1.1 g) displaying the characteristic peaks for 4-nitroaniline and benzotriazole in the ^1H nmr spectrum along with other impurities (mostly DMSO).

Benzothiazole-2-sulfenamide (4). A solution of 2-benzothiazolethione (16.7g, 0.1 mole) and NaOH (4g, 0.1 mole) in water (75 ml) and commercial bleach solution (5.25% sodium hypochlorite, 143 ml) were added simultaneously to concentrated ammonium hydroxide solution (300 ml) which had been cooled to 7°C. The addition was carried out over ~45 minutes, adding the two solutions at approximately the same rate and maintaining the temperature between 7 and 10°C. Good mechanical stirring was required to keep the copious precipitate from caking. The white precipitate was filtered and dried affording 14.77g (81%) sulfenamide 4, mp 127-28°C (lit. mp 127-28°C [49JOC921]). ^1H nmr (acetone-d_6-$CDCl_3$): δ7.75 (m, 2H), δ7.3 (m, 2H), δ4.1 (broad s, 2H). ^{13}C nmr (DMSO): δ182.2, δ154.72, δ134.34, δ125.86, δ123.23, δ121.48, δ120.79.

The crude product contained a small amount of insoluble material. Attempts to recrystallize the crude product from chloroform/petroleum ether as per the literature procedure resulted only in darkening of the product. Partial purification could be achieved by stirring the crude product in ether or chloroform and filtering the insoluble material out. When this was done one week after the product was synthesized, 1.0g of crude product yielded 0.92g (92% recovery) of 4 melting at 118-123°C. The melting point of the crude product at this point was ~116°C. After three weeks 5.0g crude product yielded 4.16g (83% recovery); after 5 weeks 3.5g gave 1.65g (47%).

Reaction of benzothiazole-2-sulfenamide with nitrobenzene. A solution of potassium t-butoxide (0.56g, 5.0 mmole) in DMSO (2.5 ml) was added dropwise to a solution of 2-benzothiazolesulfenamide (0.23g, 1.25 mmole) and nitrobenzene (0.13 ml, 1.25 mmole) in DMSO (5ml). There was an immediate formation of a deep purple color which turned brown after ~10 minutes. TLC analysis showed that the sulfenamide was consumed while most of the nitrobenzene remained. There was a small spot with the characteristic color and R_f value of 4-nitroaniline and a small spot with the correct R_f value for 2-benzothiazolethione in addition to an unidentified product spot. Neither longer reaction time nor addition of a second equivalent of sulfenamide improved the reaction.

The reaction was tried under several different conditions using 0.46g (2.5 mmole) benzothiazole-2-sulfenamide and 0.26ml (2.5 mmole) nitrobenzene. With sodium methoxide (0.27g, 5 mmole) in methanol (10 ml) there was no reaction at room temperature or at reflux (one hour); both starting materials were observed unchanged in the TLC. In neat triethylamine (10 ml) at room temperature no reaction occurred, while at reflux, a dark brown color developed; TLC showed no 4-nitroaniline product, but the sulfenamide had been partially consumed.

Acylation of benzothiazole-2-sulfenamide. A) Under Schotten-Baumann conditions: benzoyl chloride (0.39g, 2.75 mmole) was added to a slurry of benzothiazole-2-sulfenamide (4) (0.46g, 2.5 mmole) in 10% aqueous NaOH (2 ml) and the mixture was shaken vigorously for 15 minutes. The pH was adjusted to 9-10 and the precipitate was filtered and dried to yield 0.42g (91%) recovered starting material, identified by matching mp (123-24°C) and ^{1}H nmr spectrum.

B) In pyridine: benzothiazole-2-sulfenamide (1.65g, 9.07 mmole) was dissolved in pyridine (15 ml) at 0°C and benzoyl chloride (1.05 ml, 9.07 mmole) was added dropwise. After one hour at 0°C, two products were observed, R_f 0.57 and 0.17 (1:1 petroleum ether/ether). There was also a small amount of unreacted sulfenamide. Ether was added and pyridine was removed by carefully neutralizing to pH 5-6 at 5-10°C with aqueous HCl. An insoluble precipitate was

filtered out and dried to give 0.45g disulfide **5**, accounting for 30% of the starting sulfenamide. Recrystallization from benzene gave white plates, mp 178-80°C (lit. mp 179-80°C [61JOC3436]); found: 50.61%C, 2.18%H, 7.90%N; $C_{14}H_8N_4S$ requires 50.60%C, 2.41%H, 8.43%N.

The ether phase was washed, dried and evaporated and the crude product mixture was separated by flash chromatography. N-benzoylsulfenamide **9** (R_f 0.17) was obtained; yield 0.69g (27%). The product was recrystallized from 1:1 hexane/chloroform to give white plates, mp 163-64°C; found: 58.06%C, 3.00%H, 9.59%N; $C_{14}H_{10}N_2OS_2$ requires 58.74%C 3.50%H 9.79%N. Low resolution mass spectrometry: m/e = 286. ^{1}H nmr ($CDCl_3$): complex multiplet, δ8.1-7.24.

The second product (R_f 0.57) was identified by X-ray crystallography as **10**, the product of O-acylation of the conjugate base of **9**; yield 0.85g (accounting for 24% of the starting sulfenamide). The product was recrystallized from absolute ethanol to give white needles, mp 126-26.5°C, found: 63.50%C, 3.19%H, 7.04%N; $C_{21}H_{14}N_2O_2S_2$ requires 64.60%C, 3.61%H, 7.17%N. Low resolution mass spectrometry: m/e = 390. ^{1}H nmr ($CDCl_3$): δ8.26 (d, 1H); complex multiplet, δ7.26-7.94.

3.8.2 Amination with 4-Amino-1,2,4-triazoles: General Synthetic Procedure

Amination of nitrobenzenes. A solution of potassium t-butoxide (0.56g, 5.0 mmole) in DMSO (5 ml) was added

dropwise to a solution of the 4-amino-1,2,4-triazole (3.0 mmole) and the nitrobenzene (2.5 mmole) in DMSO (10 ml) over 10-15 minutes at 20-25°C. The highly colored solution was stirred at room temperature for 15 minutes, then quenched with saturated NH_4Cl (50 ml) and extracted with ether (3 x 50 ml). The combined ether phases were washed once with water (50ml), then dried ($MgSO_4$) and the solvent was removed in vacuo. The crude 4-nitroanilines (12) were purified by flash chromatography (with the exception of 12d) using 1:1 petroleum ether/diethyl ether, and recrystallized from from 50% aqueous ethanol. The yields and melting points of 12a-h are recorded in Table 3.1, elemental analyses are given in Table 3.2 and their ^1H and ^{13}C nmr spectra are reported in Tables 3.3 and 3.4 respectively.

The secondary 4-nitroanilines (18) prepared by this procedure were purified using petroleum ether/diethyl ether mixtures of varying proportions depending upon the 3- and N-substituents. If necessary, the products were further purified by recrystallization from 50% aqueous ethanol. The yields and melting points of 18a-j are given in Table 3.9, and their ^1H and ^{13}C nmr spectra are recorded in Tables 3.10 and 3.11 respectively.

The 4-nitroanilines are light to deep yellow needles with the exception of N-benzyl 4-nitroaniline (18d) which gave deep yellow plates.

3.8.3 Preparation of 4-Alkylamino-1,2,4-triazoles

4-Amino-1-methyl-1,2,4-triazole p-toluenesulfonate (15a). 4-Amino-1,2,4-triazole (0.84g, 10 mmole) and methyl p-toluenesulfonate (1.86g, 10 mmole) were dissolved in absolute ethanol (3 ml) and heated under reflux for four hours. The ethanol was evaporated to give a quantitative yield of **15a** as a white solid, mp 144-47°C. The crude product was recrystallized from 1:1 ethanol/dioxane to give 2.28g (85%) white plates, mp 151-53°C (lit. mp 157°C [66MI1]). Found: 44.57%C, 5.45%H, 20.78%N; $C_{10}H_{14}N_4O_3S$ requires 44.44%C, 5.19%H, 20.74%N. ^{1}H nmr (DMSO): δ10.1 (s, 1H, triazole H2), δ9.15 (s, 1H, triazole H4), δ7.5 (d, 2H, aryl H2,6), δ7.15 (d, 2H, aryl H3,5), δ6.6 (bs, 2H, NH_2), δ4.0 (s, 3H, N-CH_3), δ2.9 (s, 3H, Ar-CH_3). ^{13}C nmr (DMSO): δ144.97 (triazole ring), δ142.97 (Cl), δ138.10 (C4), δ128.20 (C3,5), δ125.38 (C2,6), δ38.82 (N-CH_3), δ20.74 (Ar-CH_3).

4-Amino-1-ethyl-1,2,4-triazole p-toluenesulfonate (15b). In a similar fashion, 4-amino-1,2,4-triazole (2.94g, 35 mmole) and ethyl p-toluenesulfonate (7.0g, 35 mmole) gave **15b** in quantitative yield as a light yellow oil which slowly crystallized on standing to an off-white hygroscopic solid, mp 64-70°C. (No literature melting point given [69JPR9, 66MI1]); it was used without further purification. ^{1}H nmr ($CDCl_3$): δ10.15 (s, 1H, triazole H2), δ8.65 (s, 1H, triazole H4), δ7.55 (d, 2H, aryl H2,6), δ7.0 (d, 2H, aryl H3,5), δ6.9

(bs, 2H, NH_2), δ4.15 (q, 2H, N-CH_2), δ2.3 (s, 3H, Ar-CH_3), δ1.3 (t, 3H, $CH_2\underline{CH}_3$). ^{13}C nmr ($CDCl_3$): δ145.11 (triazole ring), δ142.34 (C1), δ138.10 (C4), δ128.25 (C3,5), δ125.42 (C2,6), δ47.30 (N-CH_2), δ20.79 (Ar-CH_3), δ13.67 ($CH_2\underline{CH}_3$).

Rearrangement of 15 into 4-alkylamino-1,2,4-triazoles 16. Crude 15a (0.05 mole) was dissolved in a minimum amount of H_2O and a solution of NaOH (4.0g, 0.1 mole) dissolved in a minimum amount of H_2O was added. The solution was heated to 75°C for three hours, then evaporated to dryness in vacuo at 75°C. The solid residue was extracted with $CHCl_3$ (3 x 50 ml) and the solvent was removed in vacuo to give 2.59g (53%) N-methyl 4-amino-1,2,4-triazole (**16a**) as a light brown oil which was not purified further. (The literature reports that the product decomposes on distillation [69JPR9].)

Similarly, tosylate **15b** (6.2g, 21.8 mmole) in H_2O (6.5 ml) was treated with NaOH (1.74g, 43.6 mmole). The solution was heated to 75°C for three hours, then the pH was adjusted to 12 with NaOH and the aqueous phase was continuously extracted, first with ether and then with chloroform until no more product could be recovered. Total yield of **16b** was 1.7g (71%) light yellow waxy solid.

The ^1H and ^{13}C nmr spectra of **16a** and **b** are reported in Table 3.8.

Preparation of imines (17): general synthetic procedure. Following the procedure of Becker, et. al. [68Tl031], 4-amino-1,2,4-triazole (4.2g, 0.05 mole) and the

aldehyde or ketone (0.05 mole) were dissolved in absolute ethanol (40ml) and one drop of conc. H_2SO_4 was added. [A two- to three-fold excess was used when the carbonyl component was volatile (acetaldehyde, acetone)]. The mixture was heated to reflux for five hours (for aldehydes), or for 24 hours in the presence of 3A molecular sieves (for ketones). The crude imines were isolated by evaporation of the solvent and used without further purification. The yields of imines 17b-f are given in Table 3.5 and their ^1H and ^{13}C nmr spectra are reported in Table 3.6.

Reduction of imines (17). A) With lithium aluminum hydride: Imine 17d (0.52g, 3.0 mmole) was dissolved in THF (20 ml, distilled from CaH_2 under Ar) in the drybox. $LiAlH_4$ (0.17g, 4.5 mmole) was added in portions. After 30 minutes at room temperature, the reaction was quenched, first with ethyl acetate, followed by water. The whole was then added to NaOH solution (final pH was 12) and the aqueous phase was continuously extracted with ether for 24 hours. The ether phase was dried (Na_2SO_4) and evaporated to give 0.45g (89%) 4-benzylamino-1,2,4-triazole (16d) as a light yellow oil which slowly crystallized; mp 102-6°C (lit. 66%, mp 109-11°C [66MI1]).

B) With sodium borohydride: the preparation of N-ethyl 4-amino-1,2,4-triazole (16b) is a representative example of the general synthetic procedure. Imine 17b (4.4g, 0.04 mole) was dissolved in dry methanol (40 ml). Sodium

borohyride (1.51g, 0.04 mole) was added portionwise. After the initial vigorous gas evolution had subsided, the mixture was heated to reflux for 15 minutes. The solvent was then evaporated and the residue was dissolved in a minimum amount of 1N NaOH (final pH was 12). The solution was evaporated to dryness and the residual solids were extracted with $CHCl_3$ (3 x 50 ml). Evaporation of the solvent gave 4.4g (98%) white solid, mp 74-77°C (lit. 73%, mp 80°C [69JPR9]).

Amines 16b, c, e and f were prepared by this procedure. Yields and melting points are shown in Table 3.7; ^1H and ^{13}C nmr spectral data is given in Table 3.8

3.8.4 Amination of Other Nitroaromatics

Amination of 1-nitronaphthalene. A) 1-Nitronaphthalene (0.43g, 2.5 mmole) was added to a solution of potassium t-butoxide (0.56g, 5.0 mmole) and 4-amino-1,2,4-triazole (0.84g, 10 mmole) in DMSO (10 ml). After 15 minutes at room temperature, the reaction was worked up as described above. Three products were isolated from the crude product mixture by flash chromatography using 1:1 petroleum ether/diethyl ether. 1-Nitro-2-naphthaleneamine (**21**) was the major product: 0.17g (36%), R_f 0.23, mp 124.5-25°C (lit. mp 126-27°C [40JGU55]). After recrystallization from 50% aqueous ethanol the mp was 125-26°C. Found: 64.12%C, 4.24%H, 14.82%N; $C_{10}H_8N_2O_2$ requires 63.83%C, 4.26%H, 14.89%N. ^1H

nmr (acetone-d_6): δ8.55 (dd, 1H), δ7.86 (d, 1H), δ7.78 (dd, 1H), δ7.59 (m, 1H), δ7.36 (m, 1H, plus NH_2, broad), δ7.22 (d, 1H). ^{13}C nmr (DMSO): δ146.87, δ135.61, δ129.03, δ128.15, δ127.76, δ126.45, δ124.35, δ123.18, δ122.16, δ119.28.

Also obtained was 4-nitro-1-naphthalenamine (**22**), 0.12g (26%), mp 184.5-87°C (lit. mp 190.5-91.5°C [55OSC(3)664]). After two recrystallizations from 50% aqueous ethanol the mp was 190-91°C. Found: 63.76%C, 4.25%H, 15.02%N; $C_{10}H_8N_2O_2$ requires 63.83%C, 4.26%H, 14.89%N. ^1H nmr (acetone-d_6): δ8.94 (dd, 1H), δ8.38 (d, 1H), δ8.28 (dd, 1H), δ7.75 (m, 1H), δ7.56 (m, 1H), δ6.82 (d, 1H, plus NH_2, broad). ^{13}C nmr (DMSO): δ153.69, δ131.76, δ130.40, δ127.96, δ124.99, δ123.57, δ123.38, δ120.65, δ105.34.

The third product was 1,2-naphthofurazane (**23**), 0.13g (30%), R_f 0.58, mp 77-77.5°C (lit. mp 78-79°C [75JOU136]). After recrystallization from 50% aqueous ethanol, white needles were obtained, mp 78-79°C. Found: 70.35%C, 3.53%H, 16.24%N; $C_{10}H_6N_2O$ requires 70.59%C, 3.52%H, 16.47%N. ^1H nmr ($CDCl_3$): δ8.2 (m, 1H, H3), δ7.3 (m, 5H); ^{13}C nmr ($CDCl_3$): δ148.35, δ148.21, δ132.90, δ130.66, δ129.15, 125.54, δ121.25, δ113.11.

B) A solution of potassium t-butoxide (0.56g, 5.0 mmole) in DMSO (10 ml) was added dropwise to a solution of 1-nitronaphthalene (0.43g, 2.5 mmole) and 4-isopropylamino-1,2,4-triazole (0.38g, 3 mmole) in DMSO (10 ml) over 10-15

minutes at 25-30°C. After 15 minutes at room temperature, the reaction mixture was poured into 50 ml saturated NH_4Cl and extracted with ether (3 x 50 ml). The organic phase was washed with H_2O (50 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography (230-400 mesh silica gel, 50/50 petroleum ether/ether to give 0.54g (98%) N-isopropyl-4-nitronaphthalenamine (**22b**), mp 134-36°C. Found: 67.42%C, 6.38%H, 11.92%N; $C_{13}H_{14}N_2O_2$ requires 67.81%C, 6.13%H, 12.17%N. ^{1}H nmr ($CDCl_3$): δ9.15 (dd, 1H, H8), δ8.6 (d, 1H, H2), δ7.6-8.1 (m, 3H, H5,6,7), δ6.55 (d, 1H, H3), δ5.3 (br s, 1H, NH), δ4.0 (m, 1H, CH), δ1.5 [s, 6H, $(CH_3)_2$]. ^{13}C nmr ($CDCl_3$): δ148.89, δ134.27, δ129.64, δ127.88, δ125.54, δ124.86, δ121.59, δ119.99, δ101.42, δ44.54, δ22.46.

Amination of 2-nitronaphthalene. A solution of potassium t-butoxide (0.56g, 5.0 mmole) in DMSO (10 ml) was added dropwise to a solution of 2-nitronaphthalene (0.43g, 2.5 mmole) and 4-amino-1,2,4-triazole (0.84g, 10 mmole) in DMSO (10 ml) over 10-15 minutes at 25-30°C. After 15 minutes at room temperature, the reaction mixture was poured into 75 ml saturated NH_4Cl. An orange solid precipitated which was filtered and dried. It was recrystallized from aqueous ethanol to give 2-nitro-1-naphthalenamine (25) (70%) as orange-brown needles, mp 139.5-140.5°C (lit. mp 144°C [31RTC37]). A second recrystallization including treatment with decolorizing charcoal gave orange needles, mp 140-1°C.

Found: 63.70%C, 4.30%H, 15.70%N; $C_{10}H_8N_2O_2$ requires 63.83%C, 4.26%H, 14.89%N. ^{1}H nmr (acetone-d_6): δ8.48 (d, 1H), δ8.28 (broad s, 2H), δ8.02 (d, 1H), δ7.86 (dd, 1H), δ7.75-7.58 (m, 2H), δ7.12 (d, 1H). ^{13}C nmr (acetone-d_6): δ146.04, δ137.36, δ131.03, δ129.32, δ127.13, δ124.64, δ124.45, δ122.16, δ117.09.

Amination of nitrothiophenes. A solution of potassium t-butoxide (0.56g, 5.0 mmole) in DMSO (10 ml) was added dropwise to a solution of nitrothiophene (a mixture of 85% 2- and 15% 3-nitrothiophene) (0.32g, 2.5 mmole) and 4-amino-1,2,4-triazole (0.84g, 10 mmole) in DMSO (10 ml) over 10-15 minutes at 25-30°C. The reaction was more exothermic than usual and the temperature was controlled by means of a cool water bath. After 15 minutes at room temperature, the dark brown reaction mixture was poured into saturated NH_4Cl (75 ml). A brown-black solid precipitated which was filtered out, then the filtrate was extracted with ether (3 x 50 ml). Evaporation of the dried ether extract gave a yellow semi-solid which was recrystallized from 50% aqueous ethanol to give 54 mg (15%) 2-nitro-3-thiophenamine 27, mp 158-59°C (lit. mp 158°C [76BSF151]). Found: 33.55%C, 2.72%H, 19.04%N; $C_4H_4N_2O_2S$ requires 33.33%C, 2.78%H, 19.44%N. ^{1}H nmr ($CDCl_3$): δ7.5 (d, 1H, H5), δ6.6 (d, 1H, H4).

CHAPTER IV

SUMMARY AND CONCLUSIONS

In this investigation, we have utilized diverse chemical characteristics of the azoles in order to accomplish our synthetic objectives. In Chapter II, the ability of the azole ring carbons to be deprotonated and form lithio derivatives has been exploited for the functionalization of isothiazole. We have established a general method for the lithiation and functionalization of thiazole in a position other than the one that is normally preferred. We have utilized a great many different functional group interconversions of the isothiazole, thiazole and thiadiazole ring systems. A series of novel compounds based on the thiazole, isothiazole and 1,2,3-thiadiazole rings have been prepared and tested for fungicidal activity.

The key to the biological activity of the fungicidal compounds prepared in Chapter II is the interaction of the lone pair of electrons on the pyridine-like nitrogen with a metal atom in the active site of the enzyme. We have shown that the electron density at this nitrogen can be calculated by means of theoretical calculations, which can serve as a

predictive tool and help to guide the synthetic program. Some additional compounds based on these predictions were synthesized and submitted for testing.

Significant levels of fungicidal activity were observed for some of these compounds. However, the compounds tested to date are not active enough over a broad enough spectrum to be economically feasible. Nevertheless, these results are in agreement with our predictions and it remains to be seen whether compounds synthesized later in the program will have improved activity.

In Chapter III, we have established a general method for the direct amination of nitroarenes by a vicarious substitution reaction using 4-amino-1,2,4-triazoles. The success of this reaction relies on the ability of the azole ring to serve the functions of both the activating group and the leaving group in the vicarious substitution sequence. Thus, we have made use of the excellent leaving group ability of the 1,2,4-triazole ring, which is a result of the relatively low pKa of the pyrrole-like NH group, in order to transfer a substituent from the nitrogen to an aromatic ring. This reaction has allowed us to achieve a rather difficult transformation conveniently, in good yields and in a highly regiospecific manner.

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Letter Codes for Journal Titles

Code	Full Title
AHC	Adv. Heterocycl. Chem.
AJC	Austr. J. Chem.
BBR	Biochem. Biophys. Res. Commun.

BCJ	Bull. Chem. Soc. Jpn.
BSB	Bull. Soc. Chim. Belg.
BSF	Bull. Soc. Chim. Fr.
CB	Chem. Ber.
CC	J. Chem. Soc., Chem. Commun.
CI(L)	Chem. Ind. (London)
GEP	Ger. Pat.
HC	Chem. Heterocycl. Compd. (Weissberger-Taylor Series)
JA	J. Amer. Chem. Soc.
JCS	J. Chem. Soc.
JCS(P1)	J. Chem. Soc., Perkin Trans. 1
JCS(P2)	J. Chem. Soc., Perkin Trans. 2
JGU	J. Gen. Chem. USSR (Engl. Transl.)
JHC	J. Heterocycl. Chem.
JMC	J. Med. Chem.
JMR	J. Magn. Reson.
JOC	J. Org. Chem.
JOM	J. Organomet. Chem.
JOU	J. Org. Chem. USSR (Engl. Transl.)
JPC	J. Phys. Chem.
JPR	J. Prakt. Chem.
LA	Leibigs Ann. Chem.
MI	Miscellaneous (book or journal)
NEP	Neth. Pat.
OR	Org. React.
OSC	Org. Synth., Coll. Vol.

PIA(A)	Proc. Indan Acad. Sci., Sect. A
RCR	Russ. Chem. Rev (Engl. Transl.)
RTC	Recl. Trav. Chim. Pays-Bas
T	Tetrahedron
TL	Tetrahedron Lett.
USP	U. S. Pat.
ZOB	Zh. Obshch. Khim.

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BIOGRAPHICAL SKETCH

The author was born in December, 1950, in Fond du Lac, Wisconsin. After a few years, her family moved to Syracuse, New York, where she spent her childhood, graduating from Liverpool High School in 1969. From earliest memory, she intended to be an artist, but in her final year in high school was forced (under strong protest) to take chemistry. (It was either that or physics; chemistry seemed the lesser of two evils.) She soon saw the light and, from that time on, has been involved in chemistry in one way or another. After a two-year stint in the work force, she started her college education by attending a local community college for one year. Financial pressures forced a return to work, but she continued to go to school, taking night classes while working as a Research Technician, first for Albany Medical College, then for Stauffer Chemical Company. She obtained an Associate in Arts and Sciences degree from Westchester Community College in 1977.

Under strong urging from her mother, she finally took the plunge and moved to Florida in 1979 in order to continue work toward the bachelor's degree. She graduated cum laude from the University of North Florida in December, 1981 with a B. A. in chemistry. Two weeks later she found herself in Gainesville; the rest is history.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Alan R. Katritzky, Chairman
Kenan Professor of Organic Chemistry

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John A. Zoltewicz
Professor of Chemistry

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William M. Jones
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

David E. Richardson
Assistant Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Ben M. Dunn
Professor of Biochemistry and
Molecular Biology

This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

August, 1987

Dean, Graduate School